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(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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A METHOD for extracting quantitative information relating to an influence on a cellular response

FIELD OF INVENTION

The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the method.

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BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

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Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette *et al.*1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi *et al.*1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano *et al.*1995)].

Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. et al. 1995)] nucleus [(Khalil et al. 1992)], cytoskeleton [(Blobe et al. 1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalil et al. 1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson et al. 1996)]; and c) chemical tagging PKC b1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKCα ([Schmidt et al. 1997]) and of PKCγ and PKC ε ([Sakai et al. 1996]). The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot

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distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit (Adams *et al.*1991). The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie et al. 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is constructed for monitoring the presence of a specific molecular identity.

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Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [Carey, KL et al., The Journal of Cell Biology, Vol. 133, No. 5, p. 985-996 (1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural substrates, receptor binding and/or reporter gene expression.

DISCLOSURE OF THE INVENTION

The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilizing the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of

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the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to a method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cell or cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

The cells

In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

The mechanically intact living cell or cells could be selected from the group consisting of fungal cell or cells, such as a yeast cell or cells; invertebrate cell or cells including insect cell or cells; and vertebrate cell or cells, such as mammalian cell or cells. This cell or these cells is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact living cell is part of a matrix of identical or non-identical cells.

A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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The luminophore

The luminophore is the component which allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore is capable of associating with a component which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In yet another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore could be a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein

such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of a intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

The influence

In a preferred embodiment of the invention, the influence could be contact between the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance. The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be an deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library, can be compared to influence of known reference compounds under standardised conditions.

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The recording

In addition to the intensity, there are several parameters of fluorescence or luminescence which can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon tube.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore could be detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of

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which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation is determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

Apparatus

The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cell or cells, and thereby any change in the distribution of fluorescence in the cell or cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to

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record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

15 Quantitation of the influence

The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis).

and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic methods such as neural networks may also be used.

Nucleic acid constructs

- The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

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In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct. In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.
- In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, e.g. an isoform, or a splice variant or a homologue from another species.

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Screening program

The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to

detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

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Back-tracking of a signal transduction pathway

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

15 Construction and testing of probes

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" inframe with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a peptide linker between "GeneX" and GFP in the resulting fusion protein.

Detailed stepwise procedure:

- Identifying the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.
- Design of gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if

the gene is to be fused behind GFP, i.e. a GFP-"GeneX" fusion. If the gene is to be fused in front of GFP, i.e. a "GeneX"-GFP fusion, a stop codon must be avoided. Optionally, the full length sequence of GeneX may not be used in the fusion, but merely the part which localizes and redistributes like GeneX in response to a signal.

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In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- -Identifying a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech
 (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue Collection (Virginia).
 - Optimizing the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg²+ and K+, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

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- Cloning the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.

The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).

Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

Testing the probe

Once a DNA construct for a probe has been generated, its functionality and usefulness may be tested by subjecting it to the following tests:

- Transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localization.

The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localization is an indication of whether the probe is likely to perform well. If it 5 localizes as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localized soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken of very many copies of the plasmid, and localization will occur in time, e.g. within a few weeks, as plasmid copy number and expression level decreases. If localization does 10 not occur after prolonged time, it may be because the fusion to GFP has destroyed a localization function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it 15 could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localization, and no localization is observed, it may be because the probe should not be localized at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterization and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human geneproduct, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

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If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterization and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions it's back to the drawing board.

Developing an image-based assay technique

The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarization and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribition has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

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The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method which will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm which takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

- Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?
- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not,
 can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is

necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

10 Example: Developing a Quantitative assay for GLUT4 Translocation

GLUT4 is a member of the class of glucose transporter molecules which are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualize the glucose uptake response noninvasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualized by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantitate their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too

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large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the other artifacts. The result of this procedure is a binary image which shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

10 **Definitions**:

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In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cell or cells with substances which are known or suspected to exert and influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term "green fluorescent protein" is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie *et al.*1994)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed "modified GFP". "GFP" as used herein includes wild-type GFP derived from the jelly fish *Aequorea victoria* and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim et al. (1994). Proc.Natl.Acad.Sci. 91:12501, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from *Aequorea* Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the

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fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the coordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

The term "second messenger" is used to indicate a low molecular weight component involved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance which has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

The term "physiologically relevant" ,when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

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Th terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived froma mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different celltypes of mammalian origin e.g. hybridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, bTC6, HIT, or of hematopoietic origin, e.g. adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase. Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a

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GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKC α -GFP, PKC γ -GFP, and PKC ϵ -GFP disclosed by Schmidt et al.and Sakai et al., respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several aminoacids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an in-

termediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample which has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

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The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

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The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequ-

ence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments which serve to chemically cross-link and stabilize soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 mM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

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Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 mM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 mm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 mM forskolin (A), 50 mM forskolin (B), 1mM dbcAMP (C) and 100 mM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 mM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 mM forskolin and 100 mM IBMX (open arrow) followed by repeated washing with buffer containing 100 mM IBMX (solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 mM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 mM forskolin, open arrow, to increase [cAMP], N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 mm.

Figure 4. Dose response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

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Figure 5. Time from initiation of a response to half maximal ($t_{1/2\text{max}}$) and maximal (t_{max}) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All $t_{1/2\text{max}}$ and t_{max} values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the t_{max} values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

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Figure 6. Parallel dose response analyses of forskolin induced cAMP elevation and PKAc-F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on [cAMP], was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4 experiments expressed in arbitrary units.

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Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCa-F64L-S65T-GFP fusion. Carbachol (100 mM added at 1.0 second) induced a transient redistribution of PKCa-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

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Figure 8. BHK cells stably transfected with the hM1 receptor and PKCa-F64L-S65T-GFP fusion were treated with carbachol (1 mM, 10 mM, 100 mM). In single cells intracellular [Ca²+] was monitored simultaneously with the redistribution of PKCa-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca²+ concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the regions which offers best chance to monitor changes in the fluorescence intensity of the plasma membrane.

- Figure 9. a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 mM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.
- b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 °C.
- c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.
- d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

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Figure 10.

- a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 mm.
- b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time.

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The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

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EXAMPLE 1

5 Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways which lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the G_s or G₁ class.

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The catalytic subunit of the murine cAMP dependent protein kinase (PKAc)was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

Construction of the PKAc-F64L-S65T-GFP fusion:

15 Convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCGCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4),

5'GFP: TTggACACAAgCTTTggACACggCgCCCATgAgTAAAggAgAACTTTTC (SEQ ID NO:1),

25 3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

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The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

Transfection and cell culture conditions.

Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 mg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml⁻¹, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells) Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 mg G418/ml (*Neo* marker) and PKAc-F64L-S65T-GFP was maintained with 500 mg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human a2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 mg penicillinstreptomycin mixture ml⁻¹ and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror

and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were processed and analyzed in the following manner:.

Method 1: Stepwise procedure for quantitation of translocation of PKA:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
 - 2. The image was corrected for non-uniformity of the illumination by performing a pixel-bypixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.
 - 4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.
 - 5. The value determined in step 4 was subtracted from the image. All negative values were discarded.
 - 6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.
- 20 7. Scintillation proximity assay (SPA) for independent quantitation of cAMP:

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Method 2: Alternative method for quantitation of PKA redistribution:

- 1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.
 - 2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.
- 3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.
- 15 Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca²⁺-HEPES buffer including 100 mM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

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Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

- 25 CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 mM forskolin (n=3), 10 mM forskolin (n=4) and 50 mM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).
 - Fig. 2 shows the progression of response in time following treatment with 1 mM forskolin.

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Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 mM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behavior of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 mM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10µM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP], cells were treated with a combination of 10 mM forskolin and 100 mM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 mM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localization after removal of forskolin.

Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G_s protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic

distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARa2a and the PKA-F64L-S65T-GFP probe were treated with 10 mM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 mM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G₁ protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in [cAMP]_i (Fig. 3H).

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Fusion protein translocation correlated with [cAMP]i

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose response relationship was observed in the range from 0.01-50 mM forskolin (Fig. 6). A half maximal stimulation was observed at about 2 mM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 mM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 mM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6)

25 EXAMPLE 2

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKCα (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Taq® polymerase and the following oligonucleotide primers were used for PCR;

5 5'mPKCa: TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg (SEQ ID NO:5),

3'mPKCa: gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1),

3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-XhoI casette as described in example 1.

15 Cell Culture:

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BHK cells expressing the human M1 receptor under the control of the inducible metallothionine promoter and maintained with the dihydrofolate reductase marker were transfected with the PKC α -F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000 μ g Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKC α -F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500 μ g Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100 μ g penicillin-streptomycin mixture ml-1 and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Monitoring the PKC activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics

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CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

5 Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKC α -F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKC:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
- 2. The image was corrected for non-uniformity of the illumination by performing a pixel-bypixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.
 - 4. Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.
 - 5. The original image was masked with the edge mask from step 3 and the sum total of all pixel values is determined.

- 6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.
- 7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

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EXAMPLE 3

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway which is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

- The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.
 - a) Construction of murine ERK1 F64L-S65T-GFP fusion:
- Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:

5'ERK1: TTggACACAAgCTTTggACACCCTCAggATATggCggCggCggCggCggCTCCgggggggCgggg (SEQ ID NO:7),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAAGAACTT-TTC (SEQ ID NO:1)

5 3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+Xhol. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+Xhol. The two pairs of digested PCR products are subsequently ligated with a HindIII+Xhol digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion
 (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plasmid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

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60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Reditribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

EXAMPLE 4:

Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway which is activated by e.g. many growth factors.

- a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.
- b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localization of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

EXAMPLE 5:

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10 Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway which is induced by some members of the TGFbeta family of cytokines.

- a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc65I. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.
- b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.
- The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc

chambers in DMEM with 10% FCS to 80% confluency and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

5 90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

15 EXAMPLE 6:

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Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals which affect focal adhesions.

a) The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localized structures, identified as focal adhesion points (Fig. 11).

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A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

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EXAMPLE 7:

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

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The actin binding domain of the human alpha-actinin gene (GenBank Accession number: X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin which caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

Example 8:

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Probes for detection of p38 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

p38, a serine/thronine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.

- a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 &47) under the control of a CMV promoter.
- b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-bottom/-stop (SEQ ID NO:15). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 &65) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear within minutes in response to activation of the signal-ling pathway with e.g. anisomycin.

Example 9:

30 Probes for detection of Jnk1 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

- a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.
- b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

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Example 10:

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

30 PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylyl-cyclase/cGMP signal.

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- a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.
- b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop (SEQ ID NO: 82). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution from cyto-plasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

Example 11:

20 Probes for detection of IkappaB kinase redistribution.

Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.

IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.

a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto;

GenBank Accession number U55763) digested with EcoR1and Acc65l. This produces an EGFP-lkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-lkappaB-kinase probe and/or the lkappaB-kinase-EGFP probe should achieve a more cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

Example 12:

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Probes for detection of CDK2 redistribution.

Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds which modulate the activity of the pathway in living cells.

CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system which regulates the cell cycle.

- a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.
 - b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

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Example 13:

Probes for detection of Grk5 redistribution.

NO:42 &43) under the control of a CMV promoter.

Useful for monitoring signalling pathways involving desensitization of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.

- a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID
- b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.

30 Example 14:

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Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

- a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.
- b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/-stop (SEQ ID NO:106). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution from cytoplasmic to membrane-associated within seconds in response to activation of the T cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

Example 15:

25 Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of PI3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

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- a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-bottom/+stop (SEQ ID NO:23). The PCR product was digested with restriction enzymes Bgl2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Bgl2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.
- b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

Example 16:

Probes for detection of protein-tyrosine phosphatase redistribution.

- 20 Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.
- a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 &117) under the control of a CMV promoter.

b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP fusion (SEQ ID NO:118 &119) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma menbrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

Example 17:

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Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

- a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 &53) under the control of a CMV promoter.
 - b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4-bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 &77) under the control of a CMV promoter.

The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

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Example 18:

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways which are induced by e.g. many cytokines and growth factors.

- a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc65I. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 &55) under the control of a CMV promoter.
- b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/stop (SEQ ID NO:331). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78
 &79) under the control of a CMV promoter.
 - The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cyto-plasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

Example 19:

Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

- NFAT, an activator of transcription, is a component of signalling pathways which is involved in e.g. immune responses.
- a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID
- b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and E-coR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 &133) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

25 Example 20:

Probes for detection of NFkappaB redistribution.

NO:130 &131) under the control of a CMV promoter.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways which are responsive to a varity of inducers including cytokines, lymphokines, some immunosuppressive agents.

- a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.
 - b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

Example 21:

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Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes

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Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA. Example 22:

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of which are activated by growth factors.

- a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.
- b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/stop (SEQ ID NO:37). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

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SEQUENCE LISTING

5	(1) GENERAL INFORMATION
	(i) APPLICANT: NovoNordisk, BioImage
10	(ii) TITLE OF THE INVENTION: A Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging
	(iii) NUMBER OF SEQUENCES: 143
15	(iv) CORRESPONDENCE ADDRESS:(A) ADDRESSEE: NovoNordisk, BioImage(B) STREET: Mørkhøjbygade 28(C) CITY: Søborg
20	(D) STATE: DK (E) COUNTRY: DENMARK (F) ZIP: 2860
25	 (v) COMPUTER READABLE FORM: (A) MEDIUM TYPE: Diskette (B) COMPUTER: IBM Compatible (C) OPERATING SYSTEM: DOS (D) SOFTWARE: FastSEQ for Windows Version 2.0
30	<pre>(viii) ATTORNEY/AGENT INFORMATION: (A) NAME: , PV&P R (B) REGISTRATION NUMBER: (C) REFERENCE/DOCKET NUMBER:</pre>
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	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(2) 2010001	•
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:	•
	GTCTCGAGCC ATCATGAGCA GAAGCAAG	28
25	(2) INFORMATION FOR SEQ ID NO:18:	• •
35	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 27 base pairs (B) TYPE: nucleic acid	
40	(C) STRANDEDNESS: single	
40	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:	
45	GTGGATCCCA CTGCTGCACC TGTGCTA	27
	(2) INFORMATION FOR SEQ ID NO:19:	
50	(i) SEQUENCE CHARACTERISTICS:	
50	(A) LENGTH: 28 base pairs (B) TYPE: nucleic acid	
	<pre>(C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>	
	<u> </u>	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

	GTGGATCCTC ACTGCTGCAC CTGTGCTA	28
_	(2) INFORMATION FOR SEQ ID NO:20:	
5	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 40 base pairs (B) TYPE: nucleic acid	
10	(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:	
15	CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC	40
	(2) INFORMATION FOR SEQ ID NO:21:	
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
25		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:	
	CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC	32
30	(2) INFORMATION FOR SEQ ID NO:22:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs	
35	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
55	(D) TOPOLOGY: linear	
	(vi) ORIGINAL SOURCE:	
40	(A) ORGANISM: p85-top-C	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:	
	GGGAGATCTA TGAGTGCTGA GGGGTACCAG	30
45	(2) INFORMATION FOR SEQ ID NO:23:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 34 base pairs	
50	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
50	(D) TOPOLOGY: linear	
	(wi) providing programment, order to NO.22.	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:	34
	GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC	34 62

	(2) INFORMATION FOR SEQ ID NO:24:	
5	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	- ,
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:	
	GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC	33
15	(2) INFORMATION FOR SEQ ID NO:25:	
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:	
20	GTGGTACCCA TGACATGCTT GAGCAACGCA C	31
	(2) INFORMATION FOR SEQ ID NO:26:	-
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	· ·
35	(D) TOPOLOGY: linear	<u>.</u>
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:	
40	GTGGTACCTT ATGACATGCT TGAGCAACGC AC (2) INFORMATION FOR SEQ ID NO:27:	32
45	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:	
	GTGAATTCGT CAATGGAGCT GGAAAACATC G	31
<i></i>	(2) INFORMATION FOR SEQ ID NO:28:	
55	(i) SEQUENCE CHARACTERISTICS:	63

5	(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:	
10	GTGGATCCCT GCTGCTTCCG GTGGAGTTCG	30
10	(2) INFORMATION FOR SEQ ID NO:29:	
15	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:	
	GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	31
25	(2) INFORMATION FOR SEQ ID NO:30:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid	
30	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:	
35	GTAGATCTAC CATGGCGGC TGGATCCAGG CC	32
	(2) INFORMATION FOR SEQ ID NO:31:	
40	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:	
		31
50	(2) INFORMATION FOR SEQ ID NO:32:	J.L
55	(i) SEQUENCE CHARACTERISTICS:	
55	(A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:	
5	GTGGTACCTC ATGAGAGGGA GCCTCTGGCA G	31
	(2) INFORMATION FOR SEQ ID NO:33:	
10	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:	
	GTGAATTCAA CCATGGACAA TATGTCTATT ACG	33
20	(2) INFORMATION FOR SEQ ID NO:34:	
25	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:	
30	GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C	31
	(2) INFORMATION FOR SEQ ID NO:35:	27
35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	
40	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:	
45	GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC	32
70	(2) INFORMATION FOR SEQ ID NO:36:	
50	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:	

	GTCTCGAGGC ACCATGAGCG ACGTGGC														27		
			(2)	INF	ORMA	TION	r FOF	SEC	OID	NO:3	7:						
5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear																
10			(-,														
		(2	(i) S	EQUE	ENCE	DESC	RIPT	: NOI	SEC) ID	NO : 3	7:					
15	TGGGATCCGA GGCCGTGCTG CTGGCCG														27		
15			(2)	INF	ORMA	MOITA	I FOF	SEC) ID	NO:3	8:						
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 1896 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear																
25				OLEC		TYPE	E: cI	ANG									
	(A) NAME/KEY: Coding Sequence(B) LOCATION: 11891(D) OTHER INFORMATION:																
30		()	ci) S	EQUE	ENCE	DESC	CRIPT	CION:	: SEÇ	OID	NO:3	88:					
35									TTC Phe								48
									GGC Gly 25								96
40	G N G	aaa	a » a		C N TT	ccc	7 CC	TT A C	GGC	አ አ ሮ	CTC	N.C.C.	СТС		TTC	ΔΤС	144
									Gly								111
45									CCC Pro								192
50									AGC Ser								240
55									ATG Met								288

						67					
			TTC Phe							;	336
5			GGC Gly							:	384
10			GAG Glu							•	432
15			CAC His							•	480
			AAC Asn 165							!	528
20			GAC Asp								576
25			CCC Pro								624
30			AAC Asn								672
35			GGG Gly								720
			CGA Arg 245								768
40			GGC Gly								816
45			CCG Pro								864
50			CGC Arg		Gln						912
55	Gly			Ala			Arg		GTG Val 320		960

										68							
	GC Al	C AT a Il	C AA e Ly	G AA s Ly	G AT0 s I10 329	e Sei	C CCC	C TTO	C GAZ e Glu	A CA' u Hi: 33	s Gli	G ACC	TAC Tyl	TG Cy:	C CA S Gl 33	G CGC n Arg 5	1008
5	ACC Th	G CT r Le	C CG u Ar	G GA g Gl	n II6	C CAC ≥ Glr	ATO	C CTO	G CTC Let 345	ı Arç	C TT(C CGC	CAT His	GA(Glu 35(ı Ası	T GTC n Val	1056
10	AT(C GG e Gl	C ATO Y Ilo 35	e Ar	A GAC	C ATT	CTC Leu	G CGC Arg 360	j Ala	TC(C ACC	CTG Leu	GAA Glu 365	Ala	C ATO	G AGA E Arg	1104
15	GA7 Asp	GT(Val 370	r Ty	C ATT	r GTG P Val	G CAG	GAC Asp 375	Leu	ATG Met	GAC Glu	ACT Thr	GAC Asp 380	Leu	TAC	Lys	TTG Leu	1152
20	CTG Leu 385	ту.	A AGO	CAC Glr	G CAG	CTG Leu 390	AGC Ser	AAT Asn	GAC Asp	CAT His	ATC Ile 395	TGC Cys	TAC Tyr	TTC Phe	CTC Leu	TAC Tyr 400	1200
	CAG Gln	ATC Ile	CTC Leu	G CGG L Arg	GGC Gly 405	CTC Leu	AAG Lys	TAC Tyr	ATC Ile	CAC His 410	TCC Ser	GCC Ala	AAC Asn	GTG Val	CTC Leu 415		1248
25	CGA Arg	GAT Asp	CTA Leu	AAG Lys 420	CCC Pro	TCC Ser	AAC Asn	CTG Leu	CTC Leu 425	AGC Ser	AAC Asn	ACC Thr	ACC Thr	TGC Cys 430	GAC Asp	CTT Leu	1296
30	AAG Lys	ATT	TGT Cys 435	Asp	TTC Phe	GGC Gly	CTG Leu	GCC Ala 440	CGG Arg	ATT Ile	GCC Ala	GAT Asp	CCT Pro 445	GAG Glu	CAT His	GAC Asp	1344
35	CAC His	ACC Thr 450	GGC Gly	TTC Phe	CTG Leu	ACG Thr	GAG Glu 455	TAT Tyr	GTG Val	GCT Ala	ACG Thr	CGC Arg 460	TGG Trp	TAC Tyr	CGG Arg	GCC Ala	1392
40	CCA Pro 465	GAG Glu	ATC Ile	ATG Met	CTG Leu	AAC Asn 470	TCC Ser	AAG Lys	GGC	TAT Tyr	ACC Thr 475	AAG Lys	TCC Ser	ATC Ile	GAC Asp	ATC Ile 480	1440
	TGG Trp	TCT Ser	GTG Val	GGC Gly	TGC Cys 485	ATT Ile	CTG Leu	GCT Ala	GAG Glu	ATG Met 490	CTC Leu	TCT Ser	AAC Asn	CGG Arg	CCC Pro 495	ATC Ile	1488
45	TTC Phe	CCT Pro	GGC Gly	AAG Lys 500	CAC His	TAC Tyr	CTG Leu	Asp	CAG Gln 505	CTC Leu	AAC Asn	CAC His	Ile	CTG Leu 510	GGC Gly	ATC Ile	1536
50	CTG Leu	GGC Gly	TCC Ser 515	CCA Pro	TCC Ser	CAG (Glu .	GAC Asp 520	CTG . Leu .	AAT Asn	TGT Cys	Ile	ATC . Ile . 525	AAC Asn	ATG Met	AAG Lys	1584
55	GCC Ala	CGA Arg 530	AAC Asn	TAC Tyr	CTA Leu	GIn :	TCT (Ser :	CTG ·	CCC '	TCC . Ser	Lys '	ACC I	AAG (Lys '	GTG Val	GCT Ala	TGG Trp	1632

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		69															
		AAG Lys															1680
5		ATG Met															1728.
10		GCT Ala															1776
15		GCC Ala															1824
		GAG Glu 610															1872
20		GGA Gly						CTAG									1896
25	(2) INFORMATION FOR SEQ ID NO:39:																
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 631 amino acids(B) TYPE: amino acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear																
35	(ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal																
		()	ci) S	EQUI	ENCE	DESC	CRIP	TION	: SE	Q ID	NO:3	39:					
40	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu	
40		Glu	Leu		Gly	Asp	Val	Asn	Gly 25		Lys	Phe	Ser	Val 30		Gly	
	Glu	Gly		20 Gly	Asp	Ala	Thr			Lys	Leu	Thr			Phe	Ile	
45	Cys	Thr	35 Thr	Gly	Lys	Leu		40 Val	Pro	Trp	Pro		45 Leu	Val	Thr	Thr	
		50 Thr	Tyr	Gly	Val		55 Cys	Phe	Ser	Arg		60 Pro	Asp	His	Met		
	65 Gln	His	Asp	Phe		70 Lys	Ser	Ala	Met		75 Glu	Gly	Tyr	Val		80 Glu	
50	Arg	Thr	Ile		85 Phe	Lys	Asp	Asp	_	90 Asn	Tyr	Lys	Thr		95 Ala	Glu	
	Val	Lys		100 Glu	Gly	Asp	Thr		105 Val	Asn	Arg	Ile		110 Leu	Lys	Gly	
55	Ile	Asp	115 Phe	Lys	Glu	Asp	_		Ile	Leu	Gly		125 Lys	Leu	Glu	Tyr	
		130					135					140					

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	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	гÀг	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
5				180					185					Gly 190		
			195					200					205	Ser		
10		210	-				215	_	_			220		Leu		
	225				_	230			_		235			Tyr		240
	_				245					250				Ala	255	
15				260		_			265					Glu 270		
	-		275			_		280				_	285	Gln		
20	_	290	_			_	295				_	300	-	Glu		
	305	-				310					315			Thr		320
			•	-	325					330			_	Cys	335	
25			_	340					345					Glu 350		
		_	355		_			360					365	Ala		
30	_	370	_				375					380		Tyr Phe		
	385					390					395			Val		400
35					405					410				Cys	415	
	_	_		420					425					430 Glu		
			435					440					445	Tyr		
40 45		450	_				455	_				460	_	Ile	_	
	465					470					475			Arg		480
					485					490				Leu	495	
			_	500		_		_	505					510 Asn		
		-	515					520			-		525	Val		
50		530		_			535				_	540		Leu		
	545					550				_	555			Glu		560
55					565					570				Asp	575	
55	Leu	ALG	1112	590		_ u	u	G 111	TAT	-	чэр	0	- 111	z a u		

										• •							
	Val A		Glu 595	Glu	Pro	Phe	Thr	Phe 600	Ala	Met	Glu	Leu	Asp 605	Asp	Leu	Pro	
	Lys G	lu 1	Arg	Leu	Lys	Glu	Leu 615	Ile	Phe	Gln	Glu	Thr 620	Ala	Arg	Phe	Gln	٠.,
5	Pro G		Val	Leu	Glu	Ala 630	Pro										
			(2)	INF	ORMA	MOIT	FOF	SEC	ID	NO : 4	0:						
10		•-	(A) (B) (C)	LENG TYPE	TH: : nu NDED	1818 clei NESS	bas c ac	ingle	irs								
15		•	•	OLEC EATU		TYPE	E: cI	AAC									
20			(B)	NAM LOC OTH	ATIC	N: 3			quer	ıce							
		(x	i) s	EQUE	NCE	DESC	RIPT	CION:	SEC) ID	NO:4	10:					•
25	ATG G Met V																48
30	GTC G		Leu														96
35	GAG G	3ly															144
	TGC A		Thr	Gly		Leu	Pro	Val		Trp	Pro	Thr					192
40	CTG A Leu T 65																240
45	CAG (288
_ 50	CGC A																336
55	GTG A																384

						12				
		GAC Asp 130								432
5		TAC Tyr								480
10		ATC Ile								528
15	GTG . Val	CAG Gln							_	576
20		GTG Val								624
20		AAA Lys 210								672
25		ACC Thr								720
30		CTC Leu								768
35		ATG Met								816
40		TCG Ser								864
40		AAT Asn 290								912
45		CAC His								960
50		CGC Arg								1008
55		CCA Pro								1056

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						73					
	GAG Glu										1104
5	CAT His 370	_									1152
10	CAT His										1200
15	CTG Leu										1248
20	GTT Val										1296
20	GCC Ala										1344
25	TAT Tyr 450										1392
30	ATG Met										1440
35	CTG Leu		His								1488
40	AAT Asn										1536
40	CAC His										1584
45	AAA Lys 530										1632
50	AGG Arg										1680
55	TAT Tyr						Glu			Phe	1728

										, 4							
		ATG Met															1776
5		GAA Glu												TAA			1818
10			(2)	INI	FORMA	OITA	v FOI	R SEC	Q ID	NO:4	11:						
15		į)	(A) (B) (C)	LENC TYPE STRA	NCE (GTH: E: an ANDEI OLOGY	605 mino ONESS	amin acio S: s:	no ao i ingle	cids								
20		7)	/) FI	RAGME	CULE ENT T ENCE	(YPE	int	erna	al	Q ID	NO : 4	11:					
	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	
25	1 Val	Glu	Leu		5 Gly	Asp	Val	Asn		10 His	Lys	Phe	Ser		15 Ser	Gly	
	Glu	Gly	Glu 35	20 Gly	Asp	Ala	Thr	Tyr 40	25 Gly	Lys	Leu	Thr	Leu 45	30 Lys	Phe	Ile	
30	Cys	Thr 50		Gly	Lys	Leu	Pro		Pro	Trp	Pro	Thr 60		Val	Thr	Thr	
	Leu 65	Thr	Tyr	Gly	Val	Gln 70		Phe	Ser	Arg	Tyr 75		Asp	His	Met	Lys 80	
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
35	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
		Lys	115		_			120			_		125				
40		Asp 130					135					140					
	145	Tyr				150		_			155					160	
4.5	_	Ile			165					170					175		
45		Gln		180					185					190			
		Val	195					200					205				
50		Lys 210					215					220					
	225	Thr	мта	нта	стХ	230	mr	Leu	GTÀ	wec	235	GIU	neu	тУĽ	пÀр	240	
		Leu	Arg	Ser	Arg 245		Thr	Met	Ala	Ala 250	Ala	Ala	Ala	Ala	Gly 255	Pro	
55	Glu	Met	Val	Arg		Gln	Val	Phe	Asp			Pro	Arg	Tyr		Asn	

```
Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
     Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
                             295
                                                  300
5
     Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
                         310
                                             315
     Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
                     325
                                         330
     Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
10
                                     345
     Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
                                  360
     Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
                              375
15
     Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
                                              395
                         390
     Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
                      405
                                          410
     Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
20
                                     425
     Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
                                 440
                                                      445
      Gly Tyr Thr Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
                              455
25
     Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
                          470
                                              475
      Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
                     485
                                          490
      Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
30
                                     505
      Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
                                 520
                                                      525
      Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
                             535
                                                  540
35
      Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
                          550
                                             555
      Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
                                          570
      Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
40
                                      585
      Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
               (2) INFORMATION FOR SEQ ID NO:42:
45
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2529 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
50
              (D) TOPOLOGY: linear
```

- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
- 55 (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 1...2526

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

5	 			GAG Glu											4	8 8
10	 	 		GAC Asp											9	96
15				GCC Ala									_	_	14	14
20				CTG Leu											19	92
20				CAG Gln 70											24	10
25				AAG Lys											28	38
30				AAG Lys											3:	36
35				GAC Asp			Val								31	34
40				GAC Asp											4:	32
40	Tyr		His	AAC Asn 150	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	4:	80
45				TTC Phe											5	28
50				CAC His											5	76
55				GAC Asp			Tyr							CTG Leu	6	24

							′ ′						
										CTG Leu			672
5										TAC Tyr			720
10										GAG Glu		_	768
15										GGG Gly 270	_	_	816
20										CTG Leu			864
20										GAC Asp			912
25										CTT Leu			960
30										CAG Gln			1008
35										CTG Leu 350			1056
40					Thr	Tyr		Thr	Lys	TCC Ser			.1104
40										GAG Glu			1152
45										GCA Ala			1200
50	Val	Glu		Arg				His		CTG Leu			1248
55										AGG Arg 430			1296

		AAC Asn										1344
5		GTC Val										1392
10		CGC Arg										1440
15		CTC Leu									_	1488
		AAC Asn 500										1536
20		ACC Thr										1584
25		AAC Asn										1632
30		CTC Leu										1680
35		CTG Leu										1728
		TCA Ser 580	Asp		Gly	Leu	Ala	Val	Ile			1776
40		GGC Gly										1824
45		CAG Gln										1872
50		TAT Tyr										1920
55		GTG Val		Arg							Thr	1968

79

									79					
•				TCC Ser										2016
5				ACG Thr										2064
10				GAG Glu										2112
15				GAA Glu										2160
20				TAC Tyr 725										2208
20	_		_	GTC Val				_	_			_		2256
25				GGC Gly										2304
30				TTT Phe										2352
35				CTG Leu										2400
40				AGA Arg 805										2448
40				TCC Ser										2496
45				AAC Asn						TAG			·	2529
50		(2) IN	FORM	ATIO	N FO	R SE	DI C	NO:	43:				,

50 (2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 842 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

Carlo Contra de la Contra de Contra

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

5 (xi)	SEQUENCE	DESCRIPTION:	SEQ	ΙD	NO:43:
--------	----------	--------------	-----	----	--------

Ū		(2	, _													
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
10	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
		-	Glu 35	_	_			40	_	-			45			
	-	50	Thr	_	_		55					60				
15	65		Tyr	_		70	-			_	75		_			80
			Asp		85					90					95	
20	_		Ile	100					105					110		
		_	Phe 115					120					125			
0.5		130	Phe				135					140				
25	145	_	Asn			150					155					160
	-		Lys Leu		165					170					175	
30			Leu	180					185					190		
			195 Asp					200					205			
35		210	Ala				215					220				
33	225		Arg			230					235					240
	-		Val		245					250					255	
40				260					265					270		Phe
	_	_	275 Ile					280					285			
45		290					295					300				Arg
	305	-			-	310	_				315					320 Leu
					325					330					335	Glu
50	Lys	Gly	Lys	340 Glu	Ile	Met	Thr	Lys	345 Tyr	Leu	Thr	Pro	Lys	350 Ser	Pro	Val
	Phe	Ile	355 Ala	Gln	Val	Gly	Gln	360 Asp		Val	Ser	Gln	365 Thr		Glu	Lys
55		370					375					380				Ser
	385					390					395					400

										•						
	Val	His	Glu	Tyr	Leu 405	Arg	Gly	Glu	Pro	Phe 410	His	Glu	Tyr	Leu	Asp 415	Ser
	Met	Phe	Phe	Asp	Arg	Phe	Leu	Gln	Trp 425	Lys	Trp	Leu	Glu	Arg 430	Gln	Pro
5	Val	Thr	Lys 435		Thr	Phe	Arg	Gln 440	Tyr	Arg	Val	Leu	Gly 445	rys	Gly	Gly
	Phe	Gly 450		Val	Cys	Ala	Cys 455		Val	Arg	Ala	Thr	Gly	Lys	Met	Tyr
10	Ala 465		Lys	Arg	Leu	Glu 470		Lys	Arg	Ile	Lys 475	Lys	Arg	Lys	Gly	Glu 480
, 0		Met	Ala	Leu	Asn 485		Lys	Gln	Ile	Leu 490		Lys	Val	Asn	Ser 495	Gln
	Phe	Val	Val	Asn 500		Ala	Tyr	Ala	Tyr 505	Glu	Thr	Lys	Asp	Ala 510	Leu	Cys
15	Leu	Val	Leu 515	Thr	Ile	Met	Asn	Gly 520	Gly	Asp	Leu	Lys	Phe 525	His	Ile	Tyr
	Asn	Met 530	Gly	Asn	Pro	Gly	Phe 535	Glu	Glu	Glu	Arg	Ala 540	Leu	Phe	Tyr	Ala
20	Ala 545	Glu	Ile	Leu	Cys	Gly 550	Leu	Glu	Asp	Leu	His 555	Arg	Glu	Asn	Thr	Val 560
	Tyr	Arg	Asp	Leu	Lys 565	Pro	Glu	Asn	Ile	Leu 570	Leu	Asp	Asp	Tyr	Gly 575	His
	Ile	Arg	Ile	Ser 580	Asp	Leu	Gly	Leu	Ala 585	Val	Lys	Ile	Pro	Glu 590	Gly	Asp
25	Leu	Ile	Arg 595	Gly	Arg	Val	Gly	Thr 600	Val	Gly	Tyr	Met	Ala 605	Pro	Glu	Val
	Leu	Asn 610	Asn	Gln	Arg	Tyr	Gly 6 15	Leu	Ser	Pro	Asp	Tyr 620	Trp	Gly	Leu	Gly
30	625			_		630			Gly		635					640
	-		_		645				Val	650	_				655	
				660					Ser 665					670		
35			675					680					685			Glu
		690					695		His			700				
40	705					710			Leu		715					720
					725					730					735	Ser
			-	740				_	745			_		750		Ser
45			755					760					765			Ile
		770					775		Asn			780				
50	785			_		790					795					Eys
	_				805			_	Arg	810					815	
55				820					Phe 825		HIS	HIS	ше	830	ser	ASII
55	HIS	vaı	835	ser	ASN	ser	ınr,	840	Ser	ser						

		(2)	INE	ORMA	MOITA	1 FOF	SEC	O ID	NO:4	4:				
5	(i	(A) (B) (C)	LENC TYPE STRA	TH: E: nu ANDEI	CHARA 1902 Iclei ONESS 7: li	bas c ac S: si	se pa cid ingle	airs						
10			OLEC		TYPE	E: cI	ONA							
15	()	(B)	LOC	CATIO	EY: C ON: 1 INFOR	RMATI	L899 ION:	-		NO : 4	.4 :			
20	GTG	AGC	AAG	GGC	GAG Glu	GAG	CTG	TTC	ACC	GGG	GTG			48
25	 				GAC Asp		_							96
					GCC Ala									144
30					CTG Leu									192
35					CAG Gln 70									240
40			Phe		AAG Lys		Ala		Pro					288
45					AAG Lys									336
50					GAC Asp									384
50					GAC Asp									432
55					AAC Asn									480

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						00					
	145			150			155			160	
5		ATC Ile									528
10		CAG Gln									576
		GTG Val									624
15		AAA Lys 210									672
20		ACC Thr									720
25		CTC Leu									768
30		AAT Asn									816
30		CGA Arg									864
35		TGC Cys 290									912
40		CTA Leu									960
45		GAG Glu									1008
50		TTG Leu									1056
30		TAC Tyr								ATT Ile	1104
55		ATG Met									1152

	370			375			380			
5	TGT Cys									1200
10	AAG Lys									1248
	GAC Asp									1296
15	TAT Tyr									1344
20	GGC Gly 450									1392
25	GAA Glu									1440
	CAG Gln								_	1488
30	ATG Met									1536
35	AAA Lys									1584
40	CCA Pro 530									1632
45	TTG Leu									1680
50	GAT Asp									1728
50	GAA Glu									1776
55	AGG Arg									1824

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										85							
			595					600					605				
5					GAG Glu												1872
10					GCA Ala					TGA							1902
			(2)	INI	FORM	OITA	1 FOF	SEÇ	OID	NO : 4	15:						
15		(:	(A) (B) (C)	LENC TYPE STRA	NCE (GTH: E: an ANDEI OLOG)	633 nino NESS	amir acio S: si	no ad l ingle	cids								
20					CULE		_										
					ENT T							_					
		()	ci) S	SEQUI	ENCE	DESC	CRIPT	CION	: SE(Q ID	NO : 4	15:					
25	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	••
30	Glu	Gly	Glu 35		Asp	Ala	Thr	Tyr 40		Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
30	Cys	Thr 50		Gly	Lys	Leu	Pro 55		Pro	Trp	Pro	Thr 60		Val	Thr	Thr	•
	Leu 65		Tyr	Gly	Val	Gln 70		Phe	Ser	Arg	Tyr 75		Asp	His	Met	Lys 80	
35		His	Asp	Phe	Phe 85		Ser	Ala	Met	Pro 90		Gly	Tyr	Val	Gln 95		
	Arg	Thr	Ile		Phe	Lys	Asp	Asp	_		Tyr	Lys	Thr			Glu	
40	Val	Lys		100 Glu	Gly	qaA	Thr		105 Val	Asn	Arg	Ile		110 Leu	Lys	Gly	
40	Ile		115 Phe	Lys	Glu	Asp		120 Asn	Ile	Leu	Gly		125 Lys	Leu	Glu	Tyr	
	Asn	130 Tyr	Asn	Ser	His	Asn	135 Val	Tyr	Ile	Met		140 Asp	Lys	Gln	Lys		
45	145 Gly	Ile	Lys	Val	Asn	150 Phe	Lys	Ile	Arg	His	155 Asn	Ile	Glu	Asp	Gly	160 Ser	
	Val	Gln	Leu	Ala	165 Asp	His	Tyr	Gln	Gln	170 Asn	Thr	Pro	Ile	Gly	175 Asp	Gly	
				180	Pro				185					190			
50			195					200					205				
		210			Asn		215					220					
	225				Gly	230					235					240	
55	Gly	Leu	Arg	Ser	Arg 245	Ala	Arg	Ala	Ile	Met 250	Ser	Arg	Ser	Lys	Arg 255	Asp	

```
Asn Asn Phe Tyr Ser Val Glu Ile Gly Asp Ser Thr Phe Thr Val Leu
                                      265
      Lys Arg Tyr Gln Asn Leu Lys Pro Ile Gly Ser Gly Ala Gln Gly Ile
              275
                                  280
      Val Cys Ala Ala Tyr Asp Ala Ile Leu Glu Arg Asn Val Ala Ile Lys
 5
                              295
                                                  300
      Lys Leu Ser Arg Pro Phe Gln Asn Gln Thr His Ala Lys Arg Ala Tyr
                         310
                                              315
      Arg Glu Leu Val Leu Met Lys Cys Val Asn His Lys Asn Ile Ile Gly
10
                                         330
                      325
      Leu Leu Asn Val Phe Thr Pro Gln Lys Ser Leu Glu Glu Phe Gln Asp
                  340
                                     345
     Val Tyr Ile Val Met Glu Leu Met Asp Ala Asn Leu Cys Gln Val Ile
                                 360
15
     Gln Met Glu Leu Asp His Glu Arg Met Ser Tyr Leu Leu Tyr Gln Met
                              375
      Leu Cys Gly Ile Lys His Leu His Ser Ala Gly Ile Ile His Arg Asp
                          390
                                              395
      Leu Lys Pro Ser Asn Ile Val Val Lys Ser Asp Cys Thr Leu Lys Ile
20
                      405
                                          410
     Leu Asp Phe Gly Leu Ala Arg Thr Ala Gly Thr Ser Phe Met Met Thr
                                      425
                  420
      Pro Tyr Val Val Thr Arg Tyr Tyr Arg Ala Pro Glu Val Ile Leu Gly
                                 440
                                                      445
25
     Met Gly Tyr Lys Glu Asn Val Asp Leu Trp Ser Val Gly Cys Ile Met
                              455
                                                  460
     Gly Glu Met Val Cys His Lys Ile Leu Phe Pro Gly Arg Asp Tyr Ile
                          470
                                              475
     Asp Gln Trp Asn Lys Val Ile Glu Gln Leu Gly Thr Pro Cys Pro Glu
30
                                          490
      Phe Met Lys Lys Leu Gln Pro Thr Val Arg Thr Tyr Val Glu Asn Arg
                  500
                                      505
      Pro Lys Tyr Ala Gly Tyr Ser Phe Glu Lys Leu Phe Pro Asp Val Leu
                                  520
35
      Phe Pro Ala Asp Ser Glu His Asn Lys Leu Lys Ala Ser Gln Ala Arg
                             535
     Asp Leu Leu Ser Lys Met Leu Val Ile Asp Ala Ser Lys Arg Ile Ser
                         550
                                             555
     Val Asp Glu Ala Leu Gln His Pro Tyr Ile Asn Val Trp Tyr Asp Pro
40
                      565
                                         570
     Ser Glu Ala Glu Ala Pro Pro Pro Lys Ile Pro Asp Lys Gln Leu Asp
                                      585
     Glu Arg Glu His Thr Ile Glu Glu Trp Lys Glu Leu Ile Tyr Lys Glu
                                  600
45
      Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln
                              615
                                                  620
      Pro Ser Pro Leu Ala Gln Val Gln Gln
                          630
50
               (2) INFORMATION FOR SEQ ID NO:46:
```

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1824 base pairs
 - (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

	-	•	OLEC		TYPE	E: cI	ANO											
5		(B)	LO	CATIO	EY: C ON: I	L	1821	equer	nce								٠,	
10	()	ci) s	SEQUI	ENCE	DESC	CRIPT	CION:	SEÇ	Q ID	NO:4	16:							
	 _				GAG Glu												48	•
15					GAC Asp												96	:
20	 				GCC Ala												144	•
25					CTG Leu												192	
30					CAG Gln 70										AAG Lys 80		240	
					AAG Lys											· · · · · · · · · · · · · · · · · · ·	288	
35					AAG Lys										GAG Glu		336	
40	Lys		Glu	Gly	GAC Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu				384	
45					GAC Asp												432	
50					AAC Asn 150												480	
					TTC Phe									_			528	
55					CAC His												576	87

SUBSTITUTE SHEET (RULE 26)

						00				
		180			185			190		
5			CCC Pro							624
10			AAC Asn							672
			GGG Gly							720
15			CGA Arg 245							768
20			AAC Asn							816
25			GTG Val							864
30			ACG Thr							912
00	Phe		ATC Ile							960
35			ATG Met 325						GTT Val	1008
40			AGG Arg							1056
45			GGG Gly							1104
50			CAT His							1152
			CAT His							1200
55			GTG Val							1248

89

			405			410			415		
5	 		CAC His						_	_	1296
10	 		GCT Ala								1344
10			ATT Ile								1392
15			TTG Leu								1440
20			CTC Leu 485								1488
25	 		TCT Ser								1536
			TTT Phe							_	1584
30			GAG Glu								1632
35			GCC Ala								1680
40			CCA Pro 565								1728
45			ATA Ile								1776
5 0			CCA Pro							TGA	1824
50											

(2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 607 amino acids
 - (B) TYPE: amino acid

90

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

10	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
15	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65		Tyr	_		70	-			_	75		_			80
20			Asp		85	_				90			_		95	
	_		Ile	100		_	_	_	105		-			110		
		_	Phe 115		_			120			_		125			
25		130	Phe				135					140	_			
	145	_	Asn			150		_			155					160
30	_		Lys		165					170					175	
			Leu	180	_		-		185					190		
			Leu 195			_		200	_				205			
35		210	Asp				215					220				
	225		Ala		_	230			_		235			_		240
40			Arg		245					250					255	
	_		Glu	260		_			265					270		
45			Ser 275			_		280		_	_		285			
45		290	Thr	_		_	295	_				300	_			
	305		Gln			310					315					320
50			Lys		325					330					335	
			Pro	340					345					350		
			Leu 355					360					365			
55	Leu	Thr 370	Asp	Asp	His	Val	Gln 375	Phe	Leu	Ile	Tyr	Gln 380	Ile	Leu	Arg	Gly

```
Leu Lys Tyr Ile His Ser Ala Asp Ile Ile His Arg Asp Leu Lys Pro
     Ser Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys Ile Leu Asp Phe
                      405
                                          410
     Gly Leu Ala Arg His Thr Asp Asp Glu Met Thr Gly Tyr Val Ala Thr
                                      425
     Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Trp Met His Tyr Asn
                                  440
     Gln Thr Val Asp Ile Trp Ser Val Gly Cys Ile Met Ala Glu Leu Leu
10
                             455
                                                  460
      Thr Gly Arg Thr Leu Phe Pro Gly Thr Asp His Ile Asp Gln Leu Lys
                         470
                                              475
      Leu Ile Leu Arg Leu Val Gly Thr Pro Gly Ala Glu Leu Leu Lys Lys
                                          490
     Ile Ser Ser Glu Ser Ala Arg Asn Tyr Ile Gln Ser Leu Thr Gln Met
15
                                      505
      Pro Lys Met Asn Phe Ala Asn Val Phe Ile Gly Ala Asn Pro Leu Ala
                                  520
      Val Asp Leu Leu Glu Lys Met Leu Val Leu Asp Ser Asp Lys Arg Ile
20
                             535
      Thr Ala Ala Gln Ala Leu Ala His Ala Tyr Phe Ala Gln Tyr His Asp
                         550
                                              555
      Pro Asp Asp Glu Pro Val Ala Asp Pro Tyr Asp Gln Ser Phe Glu Ser
                      565
                                      570
25
     Arg Asp Leu Leu Ile Asp Glu Trp Lys Ser Leu Thr Tyr Asp Glu Val
                 580
                                     585
      Ile Ser Phe Val Pro Pro Pro Leu Asp Gln Glu Met Glu Ser
                                  600
30
               (2) INFORMATION FOR SEQ ID NO:48:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2907 base pairs
              (B) TYPE: nucleic acid
35
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
            (ix) FEATURE:
40
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2904
               (D) OTHER INFORMATION:
45
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:
                                                                           48
     ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
50
     GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC
                                                                           96
     Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                 20
     GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC
55
     Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
```

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						92						
		35			40			45				
5				CTG Leu							19	2
10	 			CAG Gln 70							24	0
10	 			AAG Lys							28	8
15				AAG Lys						_	33	6
20	 			GAC Asp						_	3.8	4
25	 -			GAC Asp							43	2
20				AAC Asn 150							48	0
30				TTC Phe							52	8
35				CAC His							57	6
40				GAC Asp							62	4
45				GAG Glu							67	2
				ATC Ile 230							72	0
50				AGT Ser							76	8
55				AGA Arg							81	.6

PCT/DK98/00145

						90				
		260			265			270		
5	 				TTA Leu					864
10					ATT Ile					912
					TTT Phe					960
15	 -				CCC Pro					1008
20					TCT Ser 345					1056
25	 				GAT Asp					1104
20					ATC Ile					1152
30					CTA Leu					1200
35					CTT Leu					1248
40					GTT Val 425					1296
45					GTC Val					1344
50					GTA Val					1392
50					TCG Ser					1440
55					AAA Lys					1488

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						94	•				
			485			490			495		
5			AAT Asn								1536
10			TTC Phe							_	1584
10			GTT Val								1632
15			CCA Pro								1680
20			GGT Gly 565								1728
25			GAT Asp								1776
30			GGG Gly								1824
00			ACT Thr								1872
35			CAT His								1920
40			GTG Val 645								1968
45			AAT Asn								2016
50			CAG Gln								2064
50			TTA Leu								2112
55			AGA Arg								2160

							95					
	705			710				715			720	
5						GAA Glu						2208
10						CAA Gln 745						2256.
						AAT Asn						2304
15						TCT Ser						2352
20						TTG Leu						2400
25						AGC Ser						2448
30						TTG Leu 825						2496 ':
						TGG Trp						2544 ;
35						GAT Asp						2592
40						AGC Ser						2640
45						ACT Thr						2688
50						GTA Val 905						2736
-						ACT Thr						2784
55						GAA Glu						2832

										96							
		930					935					940					
5														CTA Leu			2880
					CAG Gln 965				TGA								2907
10																	
			(2)	INI	FORM	OITA	1 FOI	SE(DID	NO:4	19:						
15		(:	(A) (B) (C)	LENG TYPI STRA	NCE (GTH: E: ar ANDEI OLOG!	968 mino ONESS	amin acio 3: si	no ao i ingle	cids								
20					CULE		_										
		7)) FI	RAGMI	ENT T	[YPE:	: int	erna	al								
		(2	ci) S	EQUI	ENCE	DESC	CRIPT	CION	SEC) ID	NO:4	19:					
25	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe		Gly	Val	Val	Pro	Ile 15	Leu	
	_	Glu	Leu	_	_	Asp	Val	Asn	_	10 His	Lys	Phe	Ser	Val		Gly	
	Glu	Gly	Glu	20 Gly	Asp	Ala	Thr	Tyr	25 Gly	Lys	Leu	Thr	Leu	30 Lys	Phe	Ile	
30	Cvs	Thr	35 Thr	Glv	Lvs	Leu	Pro	40 Val	Pro	Tro	Pro	Thr	45 Leu	Val	Thr	Thr	
		50		_	_		55			_		60					
	65		_			70	-			_	75		_	His		80	
35	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
40	Val	Lys			Gly	Asp	Thr			Asn	Arg	Ile		Leu	Lys	Gly	
40	Ile	_	115 Phe	Lys	Glu	Asp	_	120 Asn	Ile	Leu	Gly		125 Lys	Leu	Glu	Tyr	
	Asn	130 Tyr	Asn	Ser	His	Asn	135 Val	Tyr	Ile	Met	Ala	140 Asp	Lys	Gln	Lys	Asn	
45	145 Gly	Ile	Lys	Val	Asn	150 Phe	Lys	Ile	Arg	His	155 Asn	Ile	Glu	Asp	Gly	160 Ser	
					165	•				170				Gly	175		
				180					185					190			
50	Pro	vai	Leu 195	Leu	Pro	Asp	Asn	H1S 200	Tyr	Leu	Ser	Thr	205	Ser	Ala	Leu	
	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe	
	Val 225		Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240	
55		Leu	Arg	Ser			Ala	Glu	Gly	_		Tyr	Arg	Ala			
					245					250					255		

		_	_	_	1	_	~ .		_	7	_	_	•••	.	~ 1	7
	Asp	Tyr	Lys	Lys 260	Glu	Arg	GIu	GIu	Asp 265	TTE	Asp	Leu	HIS	ьеи 270	GIĄ	Asp
	Ile	Leu	Thr 275	Val	Asn	Lys	Gly	Ser 280	Leu	Val	Ala	Leu	Gly 285	Phe	Ser	Asp
5	Gly	Gln 290	Glu	Ala	Arg	Pro	Glu 295	Glu	Ile	Gly	Trp	Leu 300	Asn	Gly	Tyr	Asn
			Thr	Gly	Glu			Asp	Phe	Pro			Tyr	Val	Glu	
	305 Ile	Gly	Arg	Lys	Lys	310 Ile	Ser	Pro	Pro	Thr	315 Pro	Lys	Pro	Arg		320 Pro
10	Arg	Pro	Leu	Pro	325 Val	Ala	Pro	Gly	Ser	330 Ser	Lys	Thr	Glu	Ala	335 Asp	Val
	Glu	Gln	Gln	340 Ala	Leu	Thr	Leu	Pro	345 Asp	Leu	Ala	Glu	Gln	350 Phe	Ala	Pro
15			355 Ile					360					365			
15		370					375					380				
	Lys 385	Lys	Gly	Leu	Glu	Cys 390	Ser	Thr	Leu	Tyr	Arg 395	Thr	GIn	Ser	Ser	400
20	Asn	Leu	Ala	Glu	Leu 405	Arg	Gln	Leu	Leu	Asp	Cys	Asp	Thr	Pro	Ser 415	Val
	Asp	Leu	Glu	Met 420	Ile	Asp	Val	His	Val 425	Leu	Ala	Asp	Ala	Phe 430	Lys	Arg
	Tyr	Leu	Leu		Leu	Pro	Asn			Ile	Pro	Ala	Ala 445		Tyr	Ser
25	Glu	Met	435 Ile	Ser	Leu	Ala		440 Glu	Val	Gln	Ser			Glu	Tyr	Ile
	Gln	450 Leu	Leu	Lys	Lys	Leu	455 Ile	Arg	Ser	Pro	Ser	460 Ile	Pro	His	Gln	Tyr
	465		_	_		470	_		_		475	_,	_	_		480
30	-		Thr		485	-			-	490					495	
	Thr	Ser	Ser	Lys 500	Asn	Leu	Leu	Asn	Ala 505	Arg	Val	Leu	Ser	Glu 510	Ile	Phe
	Ser	Pro	Met 515	Leu	Phe	Arg	Phe	Ser 520	Ala	Ala	Ser	Ser	Asp 525	Asn	Thr	Glu
35	Asn	Leu 530	Ile	Lys	Val	Ile	Glu 535	Ile	Leu	Ile	Ser	Thr 540	Glu	Trp	Asn	Glu
	Arg 545		Pro	Ala	Pro	Ala 550	Leu	Pro	Pro	Lys	Pro 555	Pro	Lys	Pro	Thr	Thr 560
40		Ala	Asn	Asn			Asn	Asn	Asn			Leu	Gln	Asn	Ala 575	
40	Trp	Tyr	Trp	_	565 Asp	Ile	Ser	Arg		570 Glu	Val	Asn	Glu			Arg
	Asp	Thr	Ala	580 Asp	Gly	Thr	Phe	Leu	585 Val	Arg	Asp	Ala	Ser	590 Thr	Lys	Met
45	His	Gly	595 Asp	Tyr	Thr	Leu	Thr	600 Leu	Arg	Lys	Gly	Gly	605 Asn	Asn	Lys	Leu
	Tle	610 Lvs	Ile	Phe	His	Ara	615 Asp	Glv	Lvs	Tvr	Glv	620 Phe	Ser	Asp	Pro	Leu
	625					630					635					640
50			Ser		645					650					655	
	Leu	Ala	Gln	Tyr 660	Asn	Pro	Lys	Leu	Asp 665	Val	Lys	Leu	Leu	Tyr 670	Pro	Val
	Ser	Lys	Tyr 675	Gln	Gln	Asp	Gln	Val 680	Val	Lys	Glu	Asp	Asn 685	Ile	Glu	Ala
55	Val	Gly 690	Lys	Lys	Leu	His	Glu 695		Asn	Thr	Gln	Phe 700	Gln	Glu	Lys	Ser

	Arg 705	Glu	Tyr	Asp	Arg	Leu 710	Tyr	Glu	Glu	Tyr	Thr 715	Arg	Thr	Ser	Gln	Glu 720	
		Gln	Met	Lys	Arg 725	Thr	Ala	Ile	Glu	Ala 730	Phe	Asn	Glu	Thr	Ile 735	Lys	
5	Ile	Phe	Glu	Glu 740	Gln	Cys	Gln	Thr	Gln 745	Glu	Arg	Tyr	Ser	Lys 750	Glu	Tyr	
	Ile	Glu	Lys 755		Lys	Arg	Glu	Gly 760	Asn	Glu	Lys	Glu	Ile 765		Arg	Ile	
10	Met	His 770		Tyr	Asp	Lys	Leu 775	Lys	Ser	Arg	Ile	Ser 780	Glu	Ile	Ile	Asp	
	Ser 785	Arg	Arg	Arg	Leu	Glu 790	Glu	Asp	Leu	Lys	Lys 795	Gln	Ala	Ala	Glu	Tyr 800	
	Arg	Glu	Ile	Asp	Lys 805	Arg	Met	Asn	Ser	Ile 810	Lys	Pro	Asp	Leu	Ile 815	Gln	
15	Leu	Arg	Lys	Thr 820	Arg	Asp	Gln	Tyr	Leu 825	Met	Trp	Leu	Thr	Gln 830	Lys	Gly	
	Val	Arg	Gln 835	Lys	Lys	Leu	Asn	Glu 840	Trp	Leu	Gly	Asn	Glu 845	Asn	Thr	Glu	
20	Asp	Gln 850	Tyr	Ser	Leu	Val	Glu 855	Asp	Asp	Glu	Asp	Leu 860	Pro	His	His	Asp	•
	Glu 865	Lys	Thr	Trp	Asn	Val 870	Gly	Ser	Ser	Asn	Arg 875	Asn	Lys	Ala	Glu	Asn 880	
	Leu	Leu	Arg	Gly	Lys 885	Arg	Asp	Gly	Thr	Phe 890	Leu	Val	Arg	Glu	Ser 895	Ser	
25	Lys	Gln	Gly	Cys 900	Tyr	Ala	Cys	Ser	Val 905	Val	Val	Asp	Gly	Glu 910	Val	Lys	
	His	ĆAa	Val 915	Ile	Asn	Lys	Thr	Ala 920	Thr	Gly	Tyr	Gly	Phe 925	Ala	Glu	Pro	
30	Tyr	Asn 930	Leu	Tyr	Ser	Ser	Leu 935	Lys	Glu	Leu	Val	Leu 940	His	Tyr	Gln	His	
	Thr 945	Ser	Leu	Val	Gln	His 950	Asn	Asp	Ser	Leu	Asn 955	Val	Thr	Leu	Ala	Tyr 960	
	Pro	Val	Tyr	Ala	Gln 965	Gln	Arg	Arg									
35			(2)) INI	FORM	OITA	1 FO	R SE	Q ID	NO: !	50:						
		(:	i) SI	EQUEI	NCE (CHAR	ACTE	RIST	ICS:								
40			(B)	TYP	GTH: E: ni	ucle	ic a	cid									
					ANDE! OLOG			_	e								
45		•	ii) I ix) I		CULE	TYPI	E: cl	AND									
.0		ν.	٠		ME/KI	ev. (odi:	na S	eane	nce							
			(B) LO	CATION CA	: NC	1:	2157	cque								
50		(:	·		ENCE				: SE	Q ID	NO:	50:					
	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
55	Met 1	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	

					99					
		GAC Asp 20							· g	96
5		GGC Gly							14	: 4
10		GGC Gly							19	12
15		GGC Gly							24	:0
20		TTC Phe						_	28	8
20		TTC Phe 100							33	
25		GAG Glu							38	14
30		AAG Lys							43	2
35		AGC Ser							48	10
40		GTG Val							52	:8
40		GCC Ala 180							57	'6
45		CTG Leu			-				62	!4
50		CCC Pro							67	'2
55		GCC Ala							72	20

						100				
	CTC Leu									768
5	CCA Pro									816
10	GCT Ala									864
15	GAA Glu 290									912
20	AAA Lys									960
20	TGT Cys									1008
25	GGA Gly									1056
30	TAC Tyr									1104
35	TCC Ser 370									1152
40	TGG Trp		Leu			Glu				1200
40	GAA Glu									1248
45	CAC His									1296
50	CGA Arg									1344
55	CAC His 450									1392

	03.0	3 C C	יחיקית	an ware	y mm	aa.	<i>(</i> 17.7	7 00	CC 2	COM	COE	CC 3	TI 7 TE	3 m.c	л Ст	C	1440
												GGA Gly					1440
5												AGT Ser					1488
10										_		CCT Pro					1536
15												GCA Ala					1584
20												GAA Glu 540					1632
												GAC Asp					1680
25												AAC Asn					1728
30												GTG Val					1776
35												GAT Asp			_	_	1824
40												TGG Trp 620					1872
40												ATC Ile					1920
45												CAG Gln					1968
50												ATG Met			_		2016
55												ACA Thr					2064

										102							
					CAT His											GTA Val	2112
5					GGA Gly											TAA	2160
10			(2)	INE	FORM	ATION	ı FOF	R SE(O ID	NO : 5	51:						
		(i	(A)	LENC	NCE (GTH: E: an	719	amir	no ac									•
15					ANDEI OLOGY			_	9								
20					CULE ENT T		_										
		()	ci) S	EQUE	ENCE	DESC	CRIPT	CION	: SE() ID	NO: 5	51:				٠	
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
25	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val	Ser	Gly	
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40		Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
30	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80	
		His	Asp	Phe	Phe 85		Ser	Ala	Met	Pro 90	_	Gly	Tyr	Val	Gln 95	_	
35	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly	
40	Ile	Asp 130		Lys	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140		Leu	Glu	Tyr	
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160	
		Ile	Lys	Val	Asn 165		Lys	Ile	Arg	His 170		Ile	Glu	Asp	Gly 175	Ser	
45	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly	
			195		Pro	_		200	-				205				
50		210			Asn		215					220					
		Thr	Ala	Ala	Gly		Thr	Leu	Gly	Met		Glu	Leu	Tyr	Lys		
	225	T -		G -	7	230	a s	n 3	C -	n -	235	m1- ·	N6 = 4:	C	0	240	
					Arg 245					250					255		
55	Leu	Pro	Phe	Thr	Pro	Pro	Val		Lys	_	Leu	Leu	Gly	Trp		гÀг	

										105						
	Ser	Ala	Gly 275	Gly	Ser	Gly	Gly	Ala 280	Gly	Gly	Gly	Glu	Gln 285	Asn	Gly	Gln
	Glu	Glu 290	Lys	Trp	Cys	Glu	Lys 295	Ala	Val	Lys	Ser	Leu 300	Val	Lys	Lys	Leu
5	Lys 305	Lys	Thr	Gly	Arg	Leu 310	Asp	Glu	Leu	Glu	Lys 315	Ala	Ile	Thr	Thr	Gln 320
	Asn	Cys	Asn	Thr	Lys 325	Cys	Val	Thr	Ile	Pro 330	Ser	Thr	Cys	Ser	Glu 335	Ile
10	Trp	Gly	Leu	Ser 340	Thr	Pro	Asn	Thr	Ile 345	Asp	Gln	Trp	Asp	Thr 350	Thr	Gly
		•	355				Gln	360	_			-	365			
		370		_	_	-	Leu 375					380				
15	385	_				390	Ser				395					400
	-		_		405		Leu			410			-		415	
20				420			Glu Leu		425					430		
			435				Asn	440					445			
25		450					455					460	_			
25	465					470	Glu				475					480
	_	_			485		Gln			490					495	
30				500			Pro		505					510		
			515				Thr Asn	520					525			
35		530	_	_			535 Val		_		_	540				
55	545					550	Leu				555					560
				_	565		His			570					575	
40				580			Ala		585					590		
		_	595				Asn	600					605			
45		610					615 Gly					620				
	625	_	_			630	Ala	_			635					640
					645		Met			650					655	
50				660			Arg		665					670		
	_	_	675			_	Asn	680					685			
55		690					695 Pro					700				
	705				-	710				_	715					

		(2)	INI	FORM	OITA	1 FO	R SE	Q ID	NO:	52:				
5	((B)	LENG TYPI STRA	GTH: E: ni ANDEI	CHARA 2421 1Cle: ONESS Y: 1:	l bas ic ac S: s:	se pa cid ingle	airs						
10	-	ii) N ix) E			TYPI	E: cI	ANC							
15		(B)	LO	CATIO	EY: (DN: : ENFOR	12	2418	equer	nce					
	(:	xi) S	EQUI	ENCE	DESC	CRIPT	rion	: SEÇ	Q ID	NO:5	52:			
20	ATG GTG Met Val 1													48
25	GTC GAG Val Glu									_				96
30	GAG GGC Glu Gly													144
30	TGC ACC Cys Thr 50													192
35	CTG ACC Leu Thr 65													240
40	CAG CAC Gln His													288
45	CGC ACC Arg Thr													336
50	GTG AAG Val Lys													384
50	ATC GAC Ile Asp 130							_						432
55	AAC TAC Asn Tyr													480

	145			150		105	155			160	
5	GGC	ATC Ile									528
10		CAG Gln									576
		GTG Val									624
15		AAA Lys 210									672
20		ACC Thr	,								720
25		CTC Leu									768
30		ATG Met						_			816
		GTG Val									864
35		GCA Ala 290									912
40		GAT Asp									960
45		CCT Pro									1008
50		GTG Val									1056
- -		AGG Arg									1104
55		CAG Gln									1152

							100				
		370			375			380			
5									TCA Ser		1200
10									GAT Asp		1248
10									GGA Gly 430		1296
15									ACA Thr		1344
20								 	 GCT Ala	 	1392
25						 		 	 CAG Gln	 	1440
									ATA Ile		1488
30									CAG Gln 510		1536
35									AGG Arg		1584
40	CCA Pro								CTT Leu		1632
45									GTT Val		1680
50									CCT Pro		1728
50									GGA Gly 590		1776
55									GGA Gly		1824

107

						107					
		595			600			605			
5			GGA Gly							_	1872
10			GCC Ala								1920
	 		 TGT Cys 645	 		 	 		 	_	1968
15			GTC Val								2016
20			GGA Gly								2064
25			GAT Asp								2112
30			CAA Gln								2160
			GGC Gly 725								2208
35		Ser	GCT Ala							TTA Leu	2256
40			ATG Met								2304
45			AAA Lys								2352
50			CTC Leu								2400
			TTA Leu 805	TGA							2421

(2) INFORMATION FOR SEQ ID NO:53:

```
(i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 806 amino acids
              (B) TYPE: amino acid
 5
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
10
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
      Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
15
     Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
      Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
20
      Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
                                              75
     Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                          90
25
     Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                                      105
      Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
      Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
30
                             135
     Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                         150
                                             155
     Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                     165
                                         170
35
     Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                      185
     Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
                                                      205
     Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
40
                              215
     Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                             235
     Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
                                         250
45
     Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
                  260
                                      265
      Ile Val His Ser Leu Met Cys His Arg Gln Gly Glu Ser Glu Thr
                                  280
                                                      285
      Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
50
                              295
     Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
                          310
                                              315
     His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
                                          330
55
     Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu
                                      345
                                                          350
```

	Trp	Arg	Trp 355	Pro	Asp	Leu	His	Lys 360	Asn	Glu	Leu	Lys	His 365	Val	Lys	Tyr
	Cys	Gln 370		Ala	Phe	Asp	Leu 375		Cys	Asp	Ser	Val 380		Val	Asn	Pro
5	Tyr 385	His	Tyr	Glu	Arg	Val 390	Val	Ser	Pro	Gly	Ile 395	Asp	Leu	Ser	Gly	Leu 400
	Thr	Leu	Gln	Ser	Asn 405	Ala	Pro	Ser	Ser	Met 410	Met	Val	Lys	Asp	Glu 415	Tyr
10	Val	His	Asp	Phe 420	Glu	Gly	Gln	Pro	Ser 425	Leu	Ser	Thr	Glu	Gly 430	His	Ser
			435		Gln			440					445			
		450			Ala		455					460				
15	465				Pro	470					475					480
					Gly 485					490					495	
20				500	Gly				505					510		
		_	515		Asn			520		_		-	525	_		
25		530			Asn		535					540				
25	545				Pro	550					555					560
					Gln 565					570					575	
30				580	Ala				585					590		
		_	595		Ser			600					605	_		
35	_	610			Gly		615		-		_	620				
30	625				Cys	630				_	635			-		640
					645 Val					650					655	
40				660	Gly				665				•	670		
	_	-	675		Asp	_		680		-		-	685			_
45		690			Gln		695				_	700				
	705				Gly	710					715					720
					725 Ala					730					735	
50				740	Met				745					750		
			755		Lys			760					765			
55		770			Leu		775					780				
	785					790					795					800

Asp Pro Gln Pro Leu Asp 805

E			(2)	INE	ORMA	MOITA	1 FOF	SEC) ID	NO:5	54:						
5		(i		EQUEN													
				TYPE													
10				STRA				_	2								
		•	•	OLEC		TYPE	E: cI	ONA									
15			(B)	NAN LOC	CATIC	ON:	L3	3117	equer	ice							
20		()	ki) S	EQUE	ENCE	DESC	CRIPT	ION:	SEC) ID	NO:5	54:					
20	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
25	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	96
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	•
		GGC															144
30	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
		ACC															192
35	Cys	Thr 50	Thr	GIA	ГÀЗ	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	vai	Thr	Thr	
		ACC															240
	ьеu 65	Thr	Tyr	GIĄ	vaı	70	Cys	Pne	ser	Arg	75	Pro	Asp	HIS	Met	ьуs 80	
40																	
		CAC His														_	288
45	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336
		Thr															
	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	384
50	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly	
		GAC															432
55	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr	

		AGC Ser									4	80
5		GTG Val									5	28%
10		GCC Ala 180									5	76
15		CTG Leu									6	24
		CCC Pro									6	72
20		GCC Ala									7	20
25		TCT Ser									7	68
30		CTG Leu 260									8	16
35		CGG Arg										
		GAC Asp		Pro	Gln	Asp	Arg	Gln			9	12
40		GGC Gly									9	60
45		GAT Asp								_	10	80
50		CAG Gln 340								CGC Arg	10	56
55		CAC His									11	.04

		AAT Asn 370															1152
5		CAC His															1200
10		GAC Asp															1248
15		ATC Ile															1296
20		CTG Leu															1344
	Leu	CAG Gln 450	Gln	Lys	Gln	Val	Ser 455	Leu	Glu	Ala	Trp	Leu 460	Gln	Arg	Glu	Ala	1392
25	Gln 465	ACA Thr	Leu	Gln	Gln	Tyr 470	Arg	Val	Glu	Leu	Ala 475	Glu	Lys	His	Gln	Lys 480	1440
30		CTG Leu															1488
35		ATC Ile															1536
40		GAG Glu															1584
		ATC Ile 530															1632
45		CAG Gln															1680
50		AAC Asn															1728
55		ATC Ile															1776

						113							
	 	 _			GTG Val								1824
5					ACC Thr						GCC Ala	٠	1872
10					ACC Thr								1920
15					GAG Glu					_			1968
					TCA Ser 665								2016
20	 				ACA Thr								2064
25					AGC Ser								2112
30					GTC Val								2160
35					TGG Trp								2208
				Pro	GAC Asp 745	Lys	Val	Leu	Trp				2256
40					AAG Lys								2304
45					TTC Phe								2352 .
50					TAC Tyr								2400
55					CCG Pro								2448

							117						
			GGG Gly										2496
5			GGG Gly										2544
10			ATC Ile										2592
15			ATC Ile										2640
20			CTG Leu 885										2688
20			CTG Leu										2736
25			GAC Asp										2784
30			GCT Ala										2832
35			CCT Pro										2880
40			TAC Tyr 965	Met	Asp	Gln	Pro	Ser					2928
40			AAC Asn										2976
45			TTC Phe		Leu				Asp				3024
50	Val		TTA Leu	Arg				Ser					3072
55			GGT Gly				Ala				Ser	TGA	3120

115

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1039 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

					_	_	_		_			-		_		_
15	1			Lys	5					10					15	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
20	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65		Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
25		His	Asp	Phe	Phe 85		Ser	Ala	Met	Pro 90		Gly	Tyr	Val	Gln 95	
	Arg	Thr	Ile	Phe		Lys	Asp	Asp	Gly		Tyr	Lys	Thr	Arg 110		Glu
30	Val	Lys		Glu	Gly	Asp	Thr	Leu 120		Asn	Arg	Ile	Glu 125		Lys	Gly
30	Ile		115 Phe	Lys	Glu	Asp			Ile	Leu	Gly			Leu	Glu	Tyr
	Asn	130 Tyr	Asn	Ser	His		135 Val	Tyr	Ile	Met		140 Asp	Lys	Gln	Lys	
35	145 Glv	Ile	Lvs	Val	Asn	150 Phe	Lvs	Ile	Ara	His	155 Asn	Ile	Glu	Asp	Gly	160 Ser
	•		•		165		-		_	170					175	
				Ala 180	_		•		185					190		
40	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
45	Gly	Leu	Arg	Ser	Thr 245	Met	Ala	Gly	Trp	Ile 250	Gln	Ala	Gln	Gln	Leu 255	Gln
	Gly	Asp	Ala	Leu 260	Arg	Gln	Met	Gln	Val 265	Leu	Tyr	Gly	Gln	His 270	Phe	Pro
50	Ile	Glu	Val 275	Arg	His	Tyr	Leu	Ala 280	Gln	Trp	Ile	Glu	Ser 285	Gln	Pro	Trp
	Asp	Ala 290	Ile	Asp	Leu	Asp	Asn 295	Pro	Gln	Asp	Arg	Ala 300	Gln	Ala	Thr	Gln
	Leu 305	Leu	Glu	Gly	Leu	Val 310	Gln	Glu	Leu	Gln	Lys 3 1 5	Lys	Ala	Glu	His	Gln 320
55	Val	Gly	Glu	Asp	Gly 325	Phe	Leu	Leu	Lys	Ile 330	Lys	Leu	Gly	His	Tyr 335	Ala

	Thr	Gln	Leu	Gln 340	Lys	Thr	Tyr	Asp	Arg 345	Cys	Pro	Leu	Glu	Leu 350	Val	Arg
	Cys	Ile	Arg 355	His	Ile	Leu	Tyr	Asn 360	Glu	Gln	Arg	Leu	Val 365	Arg	Glu	Ala
5	Asn	Asn 370	Cys	Ser	Ser	Pro	Ala 375	Gly	Ile	Leu	Val	Asp 380	Ala	Met	Ser	Gln
	385					390					395		_	Leu		400
10					405					410				Gln	415	
				420					425	_				Gln 430		
			435					440					445	Glu		
15		450					455					460		Arg		
	465					470	_				475		_	His		480
20					485					490				Asp	495	
				500					505					Gly 510		
			515			_		520			_	_	525	Lys		
25		530					535					540		Glu		
	545					550		_			555			Leu 		560
30					565		_			570				Thr	575	
				580					585			_		Gln 590		
			595					600		_	_	_	605	Asn		
35		610					615					620		Gln		
	625				_	630				_	635		-	Ser	_	640
40					645					650				Thr	655	
				660					665			_		Lys 670		
4.5			675					680					685	Thr		
45		690					695	-				700		Phe		
	705					710					715			Ser		720
50	_				725				_	730				Ala	735	
				740					745					750		
<i></i>			755					760					765	Ser		
55	GIÀ	170	Tnr	гуз	GIU	Asn	175	Val	Pne	Leu	Ala	780	гÀг	Leu	Pne	Asn

	Asn 785	Ser	Ser	Ser	His	Leu 790	Glu	Asp	Tyr	Ser	⊕ <u>7</u> 795	Leu	Ser	Val	Ser	Trp 800		
		Gln	Phe	Asn	Arg 805		Asn	Leu	Pro	Gly 810		Asn	Tyr	Thr	Phe 815			
5	Gln	Trp	Phe	_		Val	Met	Glu	Val		Lys	Lys	His			Pro		
	His	Trp		820 Asp	Gly	Ala	Ile		825 Gly	Phe	Val	Asn		830 Gln	Gln	Ala		
	His	Asp	835 Leu	Leu	Ile	Asn	Lys	840 Pro	Asp	Gly	Thr	Phe	845 Leu	Leu	Arg	Phe		
10	Ser	850 Asp	Ser	Glu	Ile	Gly	855 Gly	Ile	Thr	Ile	Ala	860 Trp	Lys	Phe	Asp	Ser		
	865	-				870	_		Lys		875	_				880		
15			_		885				Leu	890					895			
15			_	900				_	905					910				
	-		915		_			920	Asp				925					
20	Thr	Pro 930	Val	Leu	Ala	Lys	Ala 935	Val	Asp	Gly	Tyr	Val 940	Lys	Pro	Gln	Ile		
	Lys 945	Gln	Val	Val	Pro	Glu 950	Phe	Val	Asn	Ala	Ser 955	Ala	Asp	Ala	Gly	Gly 960		
	Ser	Ser	Ala	Thr	Tyr 965	Met	Asp	Gln	Ala	Pro 970	Ser	Pro	Ala	Val	Cys 975	Pro		
25	Gln	Ala	Pro	Tyr 980		Met	Tyr	Pro	Gln 985		Pro	Asp	His	Val 990		Asp		
	Gln	Asp	_		Phe	Asp		_	Glu	Thr	Met				Arg	His	٠.	
	Val	Glu	995 Glu	Leu	Leu	Arg		Pro	Met	Asp	Ser		2001 qaA	Ser	Arg	Leu		
30	1	1010				-:	1015		Ser	_	3	1020	_					
	025	110	110	AIG	_	1030	1110		561		1035	Cly	501	Lea		1		
			(2)	INE	FORM	OITA	1 FOR	R SE	O ID	NO:	56:							
35		(:	i) SI	EQUE	ICE (CHARA	ACTE	RIST	CS:									
				LENC				_	airs									
40			(C)	STRA	ANDEI	ONES	3: si	ingle	9									
		/ -		40LE														
				FEAT		1151	J. CI	JIVA										
45			(A)	NAN	4Ε/KI	EY: (Codir	ng Se	equer	ıce								
				LOC														
		(2	(i) S	SEQUI	ENCE	DES	CRIPT	rion	: SE(O ID	NO : 5	56:						
50																		
									GGG Gly								48	
	1				5					10					15			
55									GTC Val								96	
	1			. 2							2							117

						110				
		20			25			30		
5	GGG Gly									144
10	GGC Gly 50									192
	AAG Lys									240
15	TAC Tyr									288
20	CAT His									336
25	GAA Glu									384
30	CTG Leu 130									432
00	TAC Tyr									480
35	AAT Asn								AAC Asn	528
40	ACC Thr									576
45	CCT Pro									624
50	TGG Trp 210									672
	TCC Ser									720
55	AAC Asn									768

PCT/DK98/00145 WO 98/45704

						119				
			245			250			255	
5			ATC							816
10			AAG Lys							864
10			TGG Trp							912
15			GAC Asp							960
20			GCG Ala 325							1008
25			CCA Pro							1056
			CCC Pro							1104
30			CAG Gln							1152
35			GAA Glu							1200
40			GTT Val 405							1248
45			ACA Thr							1296
			CCT Pro							1344
50			TGC Cys							1392
55			AGT Ser							1440 -

										120							
	465					470					475				480		
5													GAA Glu				1488
10													GGT Gly 510				1536
, -													TAC Tyr				1584
15													AAT Asn	_	_		1632
20													AGC Ser				1680
25													GGC Gly		_		1728
30													CTT Leu 590				1776
30													TTT Phe				1824
35													CCT Pro		GAG Glu	Т	1873
40	AA		(2)) INI	FORM	ATIO	N FO	R SEG	Q ID	NO:	57:						1875
45		(:	(A) (B) (C)	LENG TYPI STR	NCE (GTH: E: an ANDEN	624 mino DNES	amii acio S: s	no a d ingl	cids								
50		(-	v) F	RAGM:	CULE ENT '	TYPE	: in	tern	al	Q ID	NO:	57:					
55	1				5				_	10	_		Glu Glu	15	Arg Val		

				20					25					30		
	Lys	Gly	Gln 35		Phe	Asp	Val	Gly 40		Arg	Tyr	Thr	Gln 45		Gln	Tyr
5	Ile	Gly 50	Glu	Gly	Ala	Tyr	Gly 55	Met	Val	Ser	Ser	Ala 60		Asp	His	Val
	Arg 65	rys	Thr	Arg	Val	Ala 70	Ile	Lys	Lys	Ile	Ser 75	Pro	Phe	Glu	His	Gln 80
			Cys		85					90					95	
10			Glu	100					105					110		
			Ala 115					120				-	125			
15	_	130	Tyr	_			135					140		_		
	145		Phe			150					155					160
20			Val Cys		165					170					175	
20			Glu	180				_	185		_			190		
			195 Tyr					200					205			
25	_	210	Ile				215					220	_	_	_	
	225		Arg			230					235					240
30	His	Ile	Leu	Gly	245 Ile	Leu	Gly	Ser	Pro	250 Ser	Gln	Glu	Asp	Leu	255 Asn	Cys
	Ile	Ile	Asn	260 Met	Lys	Ala	Arg	Asn	265 Tyr	Leu	Gln	Ser	Leu	270 Pro	Ser	Lys
	Thr		275 Val	Ala	Trp	Ala		280 Leu	Phe	Pro	Lys		285 Asp	Ser	Lys	Ala
35		290 Asp	Leu	Leu	Asp		295 Met	Leu	Thr	Phe		300 Pro	Asn	Lys	Arg	
	305 Thr	Val	Glu	Glu		310 Leu	Ala	His	Pro	-	315 Leu	Glu	Gln	Tyr		320 Asp
40	Pro	Thr	Asp	Glu 340	325 Pro	Val	Ala	Glu	Glu 345	330 Pro	Phe	Thr	Phe	Asp	335 Met	Glu
	Leu	Asp	Asp		Pro	Lys	Glu	Arg 360	-	Lys	Glu	Leu	Ile 365		Gln	Glu
45	Thr	Ala 370	Arg	Phe	Gln	Pro	Gly 375	Ala	Pro	Glu	Gly	Pro 380	Gly	Arg	Ala	Met
	Ser 385	Lys	Gly	Glu	Glu	Leu 390	Phe	Thr	Gly	Val	Val 395	Pro	Ile	Leu	Val	Glu 400
			Gly		405				_	410					415	
50			Asp	420		_	_	_	425			_		430		
			Lys 435					440					445			
55		450	Val Phe				455					460				
		- 11C	T 11C	-75		4.1 a	1-1-C	FIU	سدن	СТУ	туг	val	G T I I	GIU	مدع	TILL

	4.65					470					475					400	
	465	Dho	Tur	Lvc	Λen	470	Gly	Acn	ጥህም	Laze	475	7 ~~	ת 1 ת	Glu	Val	480 Lvs	
	116	Pile	ıyı	Буз	Asp 485	Asp	GIY	ASII	TYL	490	TIIL	Arg	Ala	GIU	495	цуз	
	Phe	Glu	Glv	Asn	Thr	Len	Val	Asn	Ara		Glu	Len	Lvs	Glv		Asp	
5	FIIC	014	Gry	500	1111	200	vul	7.011	505	110	GIU	DCu	Ly 3	510		nop	
Ū	Phe	Lvs	Glu		Gly	Asn	Tle	Leu		His	Lvs	Met	Glu		Asn	Tvr	
		-1-	515		1			520	1		-1-		525	-1-		-1-	
	Asn	Ser		Asn	Val	Tvr	Ile		Ala	Asp	Lvs	Pro		Asn	Glv	Ile	
		530				- 1 -	535				-1-	540	-1-		1		
10	Lys	Val	Asn	Phe	Lys	Ile	Arq	His	Asn	Ile	Lys	Asp	Gly	Ser	Val	Gln	
	545				-	550	-				555	-	•			560	
	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	
					565					570					575		
	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu	Ser	Lys	
15				580					585					590			
	Asp	Pro		Glu	Lys	Arg	Asp		Met	Ile	Leu	Leu		Phe	Val	Thr	
			595					600		_			605		_	_	
	Ala		Gly	Ile	Thr	His	_	Met	Asp	Glu	Leu	-	Lys	Pro	Gln	Glu	
		610					615					620					
20																	
			(2)	INI	FORM	7.1.1 OI	1 F.OI	(SEC) ID	NO:5	8:						
		/ 4			70E (77 F 7 F 7											
		(]	•	_	ICE (
25					E: nu			_	IIIS								
23					MDEI												
					DLOG			_	•								
			(5)	101	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		····ca	-									
		(j	Li) N	OLE	CULE	TYPE	E: cI	ANC									
30			ix) I														
			(A)	NAN	1Ε/KI	EY: (Codin	ng Se	equer	nce							
			(B)	LO	CATIO	ON:	1	1811									
			(D)	OTI	IER]	INFO	RMAT	ON:									
35		,															
		()	(1) 5	EQUE	ENCE	DESC	CRIP.	LTON	SEC	מז נ	NO:5	8:					
	እ ጥ ር	ccc	ccc	ccc	GCG	ccc	ccc	CCC	ccc	CAC	א ייירי	CTC	CCC	ccc	CNG	GTG	48
					Ala												40
40	1	Ala	AIA	AIA	5	AIG	Ата	Gry	PIO	10	MEC	Val	Arg	Gry	15	vai	
70	-				,					10					1.7		
	TTC	GAC	GTG	GGG	CCG	CGC	TAC	ACT	ААТ	CTC	TCG	TAC	ATC	GGA	GAA	GGC	96
					Pro												
				20		5	- 3 -		25			- 1		30		- · · ·	
45																	
	GCC	TAC	GGC	ATG	GTT	TGT	TCT	GCT	TAT	GAT	AAT	CTC	AAC	AAA	GTT	CGA	144
	Ala	Tyr	Gly	Met	Val	Cys	Ser	Ala	Tyr	Asp	Asn	Leu	Asn	Lys	Val	Arg	
		-	35					40	-	-			45				
50	GTT	GCT	ATC	AAG	AAA	ATC	AGT	CCT	TTT	GAG	CAC	CAG	ACC	TAC	TGT	CAG	192
	Val	Ala	Ile	Lys	Lys	Ile	Ser	Pro	Phe	Glu	His	Gln	Thr	Tyr	Cys	Gln	
		50					55					60					
	AGA	ACC	CTG	AGA	GAG	ATA	AAA	ATC	CTA	CTG	CGC	TTC	AGA	CAT	GAG	AAC	240
EE		m\	T	A	01	т1-	T	T7 -	T	*	7	D1	7	TT 2 ~	G1.	7 ~ ~	
55		Thr	Leu	Arg	Glu	Ile 70	Lys	Ile	Leu	Leu	Arg 75	Phe	Arg	His	Glu	Asn 80	

5					GCA Ala 90				288
J					ATG Met				336
10					GAT Asp				384
15					ATA Ile				432
20					CTG Leu				480
25					CGT Arg 170				528
	-				GTA Val				576
30					GGT Gly				624
35					GAG Glu				672
40					CAG Gln				720
45					CTG Leu 250				768
40					CCG Pro			_	816
50					TCC Ser				864
55					AAG Lys				912

5			CCG Pro							960
			GCA Ala 325							1008
10			CTC Leu							1056
15			AGA Arg							1104
20			CTG Leu							1152
25			AAC Asn							1200
			TAC Tyr 405							1248
30			GTG Val							1296
35			TTC Phe							1344
40			GCC Ala						_	1392
45			GAC Asp							1440
			CTG Leu 485		 					1488
50			AAC Asn							1536
55			TAT Tyr							1584

5				AAG Lys													1632
3				TAC Tyr													1680 ~
10				AAC Asn													1728
15				AAG Lys 580													1776
20				ACT Thr									STAA				1815
			(2)) INI	FORM	OLLY	N FOR	R SE(Q ID	NO:5	59:		,				
25		(:	(A) (B) (C)	EQUEN LENC TYPI STRA	ETH: E: ar ANDEI	604 mino ONESS	amin acio S: s:	no ad i ingle	cids								:
30			Li) N	MOLE RAGMI	CULE	TYPI	E: pi	rote:									ï .
35				SEQUI													<u> </u>
	1			Ala Gly	5					10				_	15		
40		_		20 Met		_	-		25			-		30			
			35	Lys				40					45				
		50		Arg			55					60		_			
45	65 Ile	Ile	Gly	Ile		70 Asp	Ile	Ile	Arg		75 Pro	Thr	Ile	Glu		80 Met	
	Lys	Asp	Val	Tyr 100	85 Ile	Val	Gln	Asp	Leu 105	90 Met	Glu	Thr	Asp	Leu 110	95 Tyr	Lys	
50	Leu	Leu	Lys 115	Thr	Gln	His	Leu	Ser 120		Asp	His	Ile	Cys 125		Phe	Leu	
	Tyr	Gln 130		Leu	Arg	Gly	Leu 135		Tyr	Ile	His	Ser 140	Ala	Asn	Val	Leu	
55	145			Leu Cys		150					155					160	
		-73	114	Cys			Cry	L-u	тта	AL 9	VUL		٠.٠٠				405

					165					170					175	
	Asp	His	Thr	Gly 180	Phe	Leu	Thr	Glu	Tyr 185	Val	Ala	Thr	Arg	Trp 190	Tyr	Arg
5	Ala	Pro	Glu 195	Ile	Met	Leu	Asn	Ser 200	Lys	Gly	Tyr	Thr	Lys 205	Ser	Ile	Asp
	Ile	Trp 210	Ser	Val	Gly	Cys	Ile 215	Leu	Ala	Glu	Met	Leu 220	Ser	Asn	Arg	Pro
	Ile 225	Phe	Pro	Gly	Lys	His 230	Tyr	Leu	Asp	Gln	Leu 235	Asn	His	Ile	Leu	Gly 240
10	Ile	Leu	Gly	Ser	Pro 245	Ser	Gln	Glu	Asp	Leu 250	Asn	Cys	Ile	Ile	Asn 255	Leu
	Lys	Ala	Arg	Asn 260	Tyr	Leu	Leu	Ser	Leu 265	Pro	His	Lys	Asn	Lys 270	Val	Pro
15	Trp	Asn	Arg 275	Leu	Phe	Pro	Asn	Ala 280	Asp	Ser	Lys	Ala	Leu 285	Asp	Leu	Leu
	Asp	Lys 290	Met	Leu	Thr	Phe	Asn 295	Pro	His	Lys	Arg	Ile 300	Glu	Val	Glu	Gln
	Ala 305	Leu	Ala	His	Pro	Tyr 310	Leu	Glu	Gln	Tyr	Tyr 315	Asp	Pro	Ser	Asp	Glu 320
20	Pro	Ile	Ala	Glu	Ala 325	Pro	Phe	Lys	Phe	Asp 330	Met	Glu	Leu	Asp	Asp 335	Leu
	Pro	Lys	Glu	Lys 340	Leu	Lys	Glu	Leu	11e 345	Phe	Glu	Glu	Thr	Ala 350	Arg	Phe
25			355	_	_			360					365	Met		
	•	370					375	_				380		Val		
	385	=				390					395			Glu [.]		400
30					405					410				Cys	415	
	_	_		420			_		425					Leu 430		
35			435					440					445	Gln		
		450					455			_		460		Arg		
40	465		_	_	_	470		_			475					480
40		_			485			_		490				Ile	495	
				500					505					Asn 510 Gly		
45			515					520				-	525	Val		
		530					535					540		Pro		
50	545					550					555	_	_	Ser		560
50					565					570				Val	575	
				580 Thr					585					590		
55			595			٠		600			<u>.</u>	4				

(2)	INFORMATION	FOR	SEQ	ID	NO:60:
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10		(B) (C) (D) (ii) (ix)	LENG TYPI STRA TOPO	GTH: E: NI ANDER OLOGY CULE URE: ME/KI CATIO	2511 LCle: DNESS Y: 1: TYPE EY: CON: :	l bas ic ac S: s: inear E: cI Codin	se pa cid ingle r DNA ng Se 2508	airs	nce					
15		(xi)	SEQUI	ENCE	DESC	CRIPT	TION	: SE(O ID	NO : 6	50:			
20	ATG GA Met Gl 1													48
25	GAA GG Glu Gl													96
20	ATC CT	-												. 144
30	ATA GA Ile As 50	p Arg												192
35	CTG CT Leu Le 65		_											240
40	ATT CA												_	288
45	AAA CT Lys Le													336
70	AAG TC													384
50	ACG GA Thr Gl	u Glu												432
55	TGT GC Cys Al 145													480

5		AGC Ser										528
3		CCG Pro 180										576
10		GGC Gly										624
15		TAT Tyr										672
20		GAG Glu										720
25		CAG Gln										768
		TGC Cys 260										816
30		TAC Tyr									_	864
35		GCG Ala										912
40		GTC Val	Tyr	Arg	Asp	Leu	Pro	Glu	Asn			960
45		CAC His									_	1008
		GAC Asp 340										1056
50		GTC Val										1104
55		GGC Gly										1152

5				CGT Arg										1200
J				ACG Thr										1248
10				TGC Cys 420										1296
15				GAG Glu										1344
20				AAC Asn										1392
25				GAC Asp										1440
	-			TCC Ser										1488
30		_		TCC Ser 500									CAA Gln	1536
35				ATA Ile										1584
40			Gly	ACC Thr	Leu	Pro	Asp	Leu	Asn	Arg	Asn		_	1632
45				AAA Lys										1680
				AAG Lys										1728
50				AAC Asn 580										1776
55				GCC Ala										1824

5	 GTG Val 610					 	-	-		1872
	AGC Ser									1920
10	CTG Leu									1968
15	CTC Leu									2016
20	GAC Asp									2064
25	TAC Tyr 690									2112
23	ACC Thr									2160
30	GAG Glu									2208
35	AAG Lys									2256
40	AAG Lys	Lys			Val					2304
45	GAG Glu 770									2352
73	ATC Ile									2400
50	CAG Gln									2448
55	CTG Leu									2496

5		CTG Leu			TAA												2511
			(2)) IN	FORM	OITA	1 FO	R SE	Q ID	NO:	51:						
10		(:	(A) (B) (C)	LENG TYPI STR	GTH: E: ar ANDEI	836 mino ONES	ACTER amin acio S: s:	no ao i ingle	cids								
15							E: pi										
		()	ki) s	SEQUI	ENCE	DES	CRIP	rion	: SE(Q ID	NO : 6	51:					
20	Met 1	Glu	Leu	Glu	Asn 5	Ile	Val	Ala	Asn	Thr 10	Val	Leu	Leu	Lys	Ala 15	Arg	
		Gly		20					25					30			
25		Leu	35					40		_			45				
		Asp 50					55					60					•
20	65	Leu		_		70				_	75					80	
30		Gln			85					90					95		. y and
		Leu		100					105					110			
35		Ser	115					120					125				ê.
		Glu 130					135	_		_		140					
	Cys 145	Ala	GIn	ser	Val	H15	GIu	Tyr	Leu	Arg	155	GIU	Pro	Pne	HIS	160	
40		Leu	Asp	Ser	Met 165		Phe	Asp	Arg	Phe 170		Gln	Trp	Lys	Trp 175		
	Glu	Arg	Gln	Pro 180	Val	Thr	Lys	Asn	Thr 185	Phe	Arg	Gln	Tyr	Arg 190	Val	Leu	
45	Gly	Lys	Gly 195	Gly	Phe	Gly	Glu	Val 200	Cys	Ala	Cys	Gln	Val 205	Arg	Ala	Thr	
		Lys 210					215					220					
	225	Lys				230					235					240	
50		Asn			245					250	-		_		255		
		Ala		260					265			_	_	270			
55		His	275				_	280					285				
	Leu	Phe	Tyr	Ala	Ala	Glu	Ile	Leu	Cys	Gly	Leu	Glu	Asp	Leu	His	Arg	

		290					295					300				
	Glu	Asn	Thr	Val	Tyr	Arg	Asp	Leu	Lys	Pro	Glu	Asn	Ile	Leu	Leu	Asp
	305					310					315					320
	Asp	Tyr	Gly	His	Ile	Arg	Ile	Ser	Asp	Leu	Gly	Leu	Ala	Val	Lys	Ile
5					325					330					335	
	Pro	Glu	Gly	Asp	Leu	Ile	Arg	Gly	Arg	Val	Gly	Thr	Val	Gly	Tyr	Met
				340					345					350		
	Ala	Pro	Glu	Val	Leu	Asn	Asn	Gln	Arg	Tyr	Gly	Leu	Ser	Pro	Asp	Tyr
			355					360					365			
10	Trp	Gly	Leu	Gly	Cys	Leu	Ile	Tyr	Glu	Met	Ile	Glu	Gly	Gln	Ser	Pro
		370					375					380				
	Phe	Arg	Gly	Arg	Lys		ГÀг	Val	Lys	Arg		Glu	Val	Asp	Arg	
	385					390					395					400
	Val	Leu	Glu	Thr		Glu	Val	Tyr	Ser		Lys	Phe	Ser	Glu		Ala
15					405					410		_			415	
	Lys	Ser	Ile	_	Lys	Met	Leu	Leu		Lys	Asp	Ala	Lys		Arg	Leu
				420			_ •		425		_	_		430	-,	-,
	Gly	Cys		Glu	Glu	GIY	Ala		Glu	Val	Lys	Arg		Pro	Pne	Pne
	_	_	435	_	_,	_	_	440	~ 1		~ 1		445		D	D
20	Arg	Asn	Met	Asn	Pne	гÀг		ьeu	GIU	Ата	GIY		Leu	Asp	PFO	Pro
	-1	450	5	•	D	7	455	**- 7		G	T	460	11-1	T	7	T1.
		Val	Pro	Asp	Pro	470	Ala	Val	TÀT	Cys	цуS 475	Asp	vai	Leu	АБР	480
	465	Gln	Dho	602	Thr.		Tarc	Cl v	V 2 1	λαη		Λαn	цic	Thr	λen	
25	GIU	GIII	PILE	261	485	vai	nys	GIY	vai	490	Leu	Азр	птэ	1111	495	дор
23	λαν	Phe	ጥህም	Car		Dhe	Ser	Thr	Glv		Va l	Ser	Tìe	Pro		Gln
	Asp	FIIC	LYL	500	шуз	1110	501	****	505	561	141	UC1	-1-0	510		0111
	Δen	Glu	Met		Glu	Thr	Glu	Cvs		Lvs	Glu	Leu	Asn		Phe	Glv
	71011	014	515		014			520		_, _	014		525			,
30	Pro	Asn		Thr	Leu	Pro	Pro		Leu	Asn	Arq	Asn		Pro	Pro	Glu
		530	2				535	-			_	540				
	Pro	Pro	Lys	Lys	Gly	Leu	Leu	Gln	Arg	Leu	Phe	Lys	Arg	Gln	His	Gln
	545		-	_	=	550					555					560
	Asn	Asn	Ser	Lys	Ser	Ser	Pro	Ser	Ser	Lys	Thr	Ser	Phe	Asn	His	His
35					565					570					575	
	Ile	Asn	Ser	Asn	His	Val	Ser	Ser	Asn	Ser	Thr	Gly	Ser	Ser	Arg	Asp
				580					585					590		
	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly
			595										605			
40	Val	Val	Pro	Ile	Leu	Val		Leu	Asp	Gly	Asp		Asn	Gly	His	Lys
		610	_				615			_		620	_		_	_
		Ser	Val	Ser	Gly		Gly	Glu	GIY	Asp		Thr	Tyr	GIY	гàг	
	625	_	_	-1	- 3	630		m\	~ 3	.	635		**- 7	D	/D	640
45	Thr	Leu	гуз	Pne		Cys	Thr	Thr	GIY		ьeu	Pro	vaı	Pro		PIO
45	m1	•	*** 3		645	.	m\	m	a 1	650	a1-	~	Dh.	C	655	т
	Thr	Leu	vaı	660	THE	Leu	Int	TAL	665	vai	GIII	Cys	Pne	670	Arg	TÀT
	Dro	Asp	ніс		Two	Cln	Uic	λαν		Dhe	Tuc	Car	713		Dro	Glu
	PIO	ASP	675	Mec	Буз	GIII	птэ	680	PILE	PIIC	пув	261	685	MEC	FIO	Olu
50	Glv	Tyr		Gln	Glu	Δτα	Thr		Dhe	Dhe	Lve	Δsn		Glv	Asn	Tvr
50	Gry	690	Val	0111	Olu	nr 9	695	110	1110	1110	БуЗ	700	1100	O ₁		-1-
	Lv≈	Thr	Ara	Ala	Glu	Val		Phe	Glu	Glv	Asp		Leu	Val	Asn	Ara
	705		9			710	-, -			1	715					720
		Glu	Leu	Lys	Gly		Asp	Phe	Lys	Glu		Gly	Asn	Ile	Leu	
55				•	725		-		•	730	•	-			735	-
	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala

										.00								
				740					745					750				
	Asp	Lys	Gln 755	Lys	Asn	Gly	Ile	Lys 760	Val	Asn	Phe	Lys	Ile 765	Arg	His	Asn		
5	Ile	Glu 770	Asp	Gly	Ser	Val	Gln 775	Leu	Ala	Asp	His	Tyr 780	Gln	Gln	Asn	Thr	•	
	Pro 785	Ile	Gly	Asp	Gly	Pro 790	Val	Leu	Leu	Pro	Asp 795	Asn	His	Tyr	Leu	Ser 800		
	Thr	Gln	Ser	Ala	Leu 805	Ser	Lys	Asp	Pro	Asn 810	Glu	Lys	Arg	Asp	His 815	Met		
10				820	Phe	Val	Thr	Ala	Ala 825	Gly	Ile	Thr	Leu	Gly 830	Met	Asp		
	Glu	Leu	Tyr 835	Lys														
15			(2)	INI	FORM	OITA	1 FO	R SEC	Q ID	NO:6	52:							
20		(3	(A) (B) (C)	LENC TYPE STRA	ETH: E: nu ANDEI	CHARA 1893 aclei ONESS Y: li	B bas ic ac B: si	se pa cid ingle	airs									
25				OLEC FEATU		TYPE	E: cI	ANC										
			(B)	LO	CATIO	EY: C ON: 3 INFOR	L :	1890	equer	nce								
30		()	ci) S	SEQUE	ENCE	DESC	CRIPT	CION	: SE(Q ID	NO : 6	52:						
35									AAT Asn								48	
33									CGA Arg 25							_	96	
40									TGC Cys								144	
45									CTA Leu							_	192	
50	*								GAG Glu								240	
									TTG Leu								288	
55	TCC	CTA	GAA	GAA	TTT	CAA	GAT	GTT	TAC	ATA	GTC	ATG	GAG	CTC	ATG	GAT	336	1.3
																		1

										134							
	Ser	Leu	Glu	Glu 100	Phe	Gln	Asp	Val	Tyr 105	Ile	Val	Met	Glu	Leu 110	Met	Asp	
5				TGC Cys													384
10				CTC Leu													432
15				ATT Ile													480
.0				ACT Thr													528
20				TTT Phe 180													576
25				GTC Val													624
30				GGG Gly													672
35				AGG Arg												_	720
				CCA Pro												_	768
40				GTT Val 260													816
45				CCT Pro													864
50				AGT Ser													912
55				AAA Lys													960
	ATC	AAT	GTC	TGG	TAT	GAT	CCT	TCT	GAA	GCA	GAA	GCT	CCA	CCA	CCA	AAG	1008

										133							
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys	
	ATC	CCT	GAC	AAG	CAG	TTA	GAT	GAA	AGG	GAA	CAC	ACA	ATA	GAA	GAG	TGG	1056
5					Gln												
	AAA	GAA	TTG	ATA	TAT	AAG	GAA	GTT	ATG	GAC	TTG	GAG	GAG	AGA	ACC	AAG	1104
	Lys	Glu	Leu	Ile	Tyr	Lys	Glu	Val	Met	Asp	Leu	Glu	Glu	Arg	Thr	Lys	
10			355					360					365				
					CGG												1152
	ASII	370	vaı	TIE	Arg	GIY	375	PIO	ser	PLO	Leu	380	GIII	vai	GIII	GIII	
15		J , c															
	TGG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	1200
	Trp	Asp	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	
	385					390					395					400	
20	N.C.C	aaa	CTC	стс	CCC	איזיכי	СТС	CTC	CAC	CTG	GAC	ccc	GAC	GTA	אאר	GGC	1248
20					Pro												1240
					405					410		1			415	1	
					GTG												1296
25	His	Lys	Phe		Val	Ser	Gly	Glu	_	Glu	Gly	Asp	Ala		Tyr	Gly	
				420					425					430			
	AAG	CTG	ACC	CTG	AAG	TTC	ATC	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	1344
	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	
30			435					440					445				
											~~~	a <b>m</b> a	a. a	<b>m</b> aa	mma	* 00	1202
					GTG Val												1392
	пр	450	1111	neu	Vai	****	455	пса	1111	T Y T	Cry	460	<b>G111</b>	Cys	1110	001	
35						-											
					CAC												1440
	_	Tyr	Pro	Asp	His		Lys	Gln	His	Asp		Phe	Lys	Ser	Ala		
	465					470					475					480	
40	CCC	GAA	GGC	TAC	GTC	CAG	GAG	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	1488
	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	
					485					490					495		
							~~~				~~~		~~~		ama	ama.	1536
45					CGC Arg												1536
40	HOIL	LYL	БУЗ	500	AL 9	AIG	Olu	vai	505	FIIC	Gru	Oly	A3D	510	Dea	Vul	
	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	1584
	Asn	Arg		Glu	Leu	Lys	Gly		Asp	Phe	Lys	Glu		Gly	Asn	Ile	
50			515					520					525				
	СТС	GGG	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	1632
					Leu												
		530		-			535		-			540			•		
55					ar -						a=+		 -			996	1600
	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGC	ATC	AAG	GTG	AAC	TTC	AAG	A.L.C.	CGC	1680

										130							
	Met 545	Ala	Asp	Lys	Gln	Lys 550	Asn	Gly	Ile	Lys	Val 555	Asn	Phe	Lys	Ile	Arg 560	
5									CAG Gln								1728
10									GTG Val 585								1776
1 E									AAA Lys								1824
15									ACC Thr								1872
20				CTG Leu			TAA										1893
25									Q ID	NO : 6	53:						
30		(:	(A) (B) (C)	LENG TYPE STRA	ETH: E: ar ANDEI	630 mino ONESS	ACTER amin acio S: s: inear	no ao i ingle	cids								
35		7)	/) FI	RAGMI	ENT T	[YPE	E: pi : int	erna		Q ID	NO : 6	53:					
	Met 1	Ser		Ser					Asn						Ile 15	Gly	
40				20					Arg 25					30			
			35					40	Cys				45				
45		50					55	_	Leu			60					
	65					70	_		Glu		75					80	
50			_		85		_		Leu	90					95		
50				100			-		Tyr 105 Met					110			
			115	_				120					125				
55		130					135		Cys			140					
	Ala	GIĀ	тте	тте	HIS	arg	Asp	ьeu	Lys	Pro	ser	ASN	тте	vaı	val	пур	40

	145					150					155					160
	Ser	Asp	Cys	Thr	Leu 165	Lys	Ile	Leu	Asp	Phe 170	Gly	Leu	Ala	Arg	Thr 175	Ala
5	Gly	Thr	Ser	Phe 180	Met	Met	Thr	Pro	Tyr 185	Val	Val	Thr	Arg	Tyr 190	Tyr	Arg
	Ala	Pro	Glu 195	Val	Ile	Leu	Gly	Met 200	Gly	Tyr	Lys	Glu	Asn 205	Val	Asp	Leu
	Trp	Ser 210	Val	Gly	Cys	Ile	Met 215	Gly	Glu	Met	Val	Cys 220	His	Lys	Ile	Leu
10	Phe 225	Pro	Gly	Arg	Asp	Tyr 230	Ile	Asp	Gln	Trp	Asn 235	Lys	Val	Ile	Glu	Gln 240
	Leu	Gly	Thr	Pro	Cys 245	Pro	Glu	Phe	Met	Lys 250	Lys	Leu	Gln	Pro	Thr 255	Val
15	Arg	Thr	Tyr	Val 260	Glu	Asn	Arg	Pro	Lys 265	Tyr	Ala	Gly	Tyr	Ser 270	Phe	Glu
	Lys	Leu	Phe 275	Pro	Asp	Val	Leu	Phe 280	Pro	Ala	Asp	Ser	Glu 285	His	Asn	Lys
		290		Ser			295	_				300				
20	305			Lys		310			_		315					320
				Trp	325	_				330					335	
25			_	Lys 340					345					350		
	_		355	Ile	-	_		360		_			365	_		
		370		Ile	_	_	375					380				
30	385	-		Pro		390					395					400
		_		Val	405					410	_		_		415	
35				Ser 420					425					430		
	_		435	Leu	-			440			-	-	445			
40	_	450		Leu			455			_	_	460				
40	465	-		Asp Tyr		470	_				475					480
				Thr	485					490					495	
45	•			500 Glu					505					510		
			515	Lys				520	-				525			
50		530		Lys			535					540			_	
	545			Glu		550					555		•			560
				Ile	5 65					570					575	
55				580 Gln	_				585				_	590		
									4 -	_				4 -		_

										100								
5		Met 610 Asp					Phe 615	600 Val	Thr	Ala	Ala	Gly 620	605 Ile	Thr	Leu	Gly		
			(2)	INE	FORM	MOITA	I FOF	R SEC	Q ID	NO : 6	54:							
10		(i	(A) (B) (C)	LENC TYPE STRA	ICE (GTH: E: nu ANDEI OLOG)	1821 nclei ONESS	bas c ac	se pa cid ingle	airs									
15			li) N lx) E		CULE JRE:	TYPE	E: cI	ANC										
20		()	(B) (D)	LOC	ME/KECATION HER DENCE	ON:]	LI	1818 [ON:			NO : 6	54:						
25		TCT Ser															48	
30		TGG Trp						_									96	
25		GCC Ala															144	
35		GTG Val 50														CAT . His	192	
40		AAA Lys														_	240	
45		AAT Asn															288	
50		GAA Glu															336	
		AAC Asn															384	
55	TTC	CTT	ATC	TAC	CAA	ATT	CTC	CGA	GGT	CTA	AAG	TAT	ATA	CAT	TCA	GCT	432	13

PCT/DK98/00145

										133							
	Phe	Leu 130	Ile	Tyr	Gln	Ile	Leu 135	Arg	Gly	Leu	Lys	Tyr 140	Ile	His	Ser	Ala	
5												CTA Leu					480
10												GCT Ala					528
15												TAC Tyr					576
15												GTT Val					624
20			Cys									AGA Arg 220					672
25												TTA Leu					720
30												TCA Ser					768
0.5												ATG Met					816
35												TTG Leu					864
40												GCC Ala 300					912
45												GAT Asp					960
50												CTC Leu					1008
 .					Thr					Ile		TTT Phe					1056
. 55	CTT	GAC	CAA	GAA	GAG	ATG	GAG	TCC	GAG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	1104

	Leu	Asp	Gln 355	Glu	Glu	Met	Glu	Ser 360	Glu	Asp	Pro	Pro	Val 365	Ala	Thr	Met	
_				GGC												_	1152
5	Val	370	гуѕ	Gly	GIU	GIU	ьец 375	Pne	Thr	GIY	vai	380	Pro	11e	Leu	val	
				GGC													1200
10	385	ьeu	Asp	Gly	Asp	390	ASII	GIY	HIS	гуѕ	395	ser	vai	ser	GIY	400	
				GAT Asp										-			1248
15	V-1		1		405		-1 -	2	-1-	410					415	-1	
15				AAG													1296
	Thr	Thr	GIÀ	Lys 420	Leu	Pro	Val	Pro	125	Pro	Thr	Leu	Val	Thr 430	Thr	Leu	
20				GTG Val												_	1344
	1111	ıyı	435	vai	GIII	Суз	FIIC	440	Arg	TYL	PIO	Asp	445	Mec	БуБ	GIII	
25				TTC Phe													1392
		450			-		455				•	460					
				TTC Phe													1440
30	465	116	PIIC	rne	цуз	470	App	GIY	ASII	lyr	475	1111	ALG	AIG	Giu	480	
				GGC Gly											_	_	1488
35	1			-	485					490				-	495		
00				GAG													1536
	Asp	Pne	гуз	Glu 500	Asp	GIY	ASII	тте	505	GIÀ	HIS	гуѕ	Leu	510	ıyı	ASII	
40				CAC His													1584
	-1-		515				-1-	520			<u>-</u> -	-1 -	525	_, _		1	
45				AAC													1632
45	Ile	Lys 530	Val	Asn	Pne	Lys	11e 535	Arg	His	Asn	Ile	G1u 540	Asp	GIY	Ser	Val	
				GAC Asp													1680
50	545	200		p	*****	550	0111	J111	HOII		555	***	Cry	p	-11	560	
				CCC													1728
E.F.	val	neu	ьeu	Pro	565	ASN	пта	ıyr	ьeu	570	IIIT	GIH	ser	нта	575	Ser	
55	AAA	GAC	ccc	AAC	GAG	AAG	CGC	GAT	CAC	ATG	GTC	CTG	CTG	GAG	TTC	GTG	1776

										141							
	Lys	Asp	Pro	Asn 580	Glu	Lys	Arg	Asp	His 585	Met	Val	Leu	Leu	Glu 590	Phe	Val	
5				GGG Gly											TAA		1821
40		•	(2)	INI	FORM	OITA	1 FOF	R SE	O ID	NO : 6	55:						
10		(i	(A) (B)	EQUEI LENC TYPI STR <i>I</i>	GTH: E: ar	606 mino	amir acid	no ad	cids								
15			(D)	TOPO	DLOG:	Y: 15	inear	r									
				MOLEC RAGMI			_										
20		(2	ki) S	SEQUI	ENCE	DESC	CRIP	rion	: SE	Q ID	NO : 6	55:					
	Met 1	Ser	Gln	Glu	Arg 5	Pro	Thr	Phe	Tyr	Arg 10	Gln	Glu	Leu	Asn	Lys 15	Thr	
25	Ile	Trp	Glu	Val 20	Pro	Glu	Arg	Tyr	Gln 25	Asn	Leu	Ser	Pro	Val 30	Gly	Ser	e.
	Gly	Ala	Tyr 35	Gly	Ser	Val	Cys	Ala 40	Ala	Phe	Asp	Thr	Lys 45	Thr	Gly	Leu	
	Arg	Väl 50	Ala	Val	rys	Lys	Leu 55	Ser	Arg	Pro	Phe	Gln 60	Ser	Ile	Ile	His	
30	Ala 65	Lys	Arg	Thr	Tyr	Arg 70	Glu	Leu	Arg	Leu	Leu 75	Lys	His	Met	Lys	His 80	
	Glu	Asn	Val	Ile	Gly 85	Leu	Leu	Asp	Val	Phe 90	Thr	Pro	Ala	Arg	Ser 95	Leu	
35	Glu	Glu	Phe	Asn 100	Asp	Val	Tyr	Leu	Val 105	Thr	His	Leu	Met	Gly 110	Ala	Asp	
			115	Ile				120					125				·
		130		Tyr			135					140					
40	Asp 145	Ile	Ile	His	Arg	Asp 150	Leu	Lys	Pro	Ser	Asn 155	Leu	Ala	Val	Asn	Glu 160	
	Asp	Cys	Glu	Leu	Lys 165	Ile	Leu	Asp	Phe	Gly 170	Leu	Ala	Arg	His	Thr 175	Asp	
45	Asp	Glu	Met	Thr 180	Gly	Tyr	Val	Ala	Thr 185	Arg	Trp	туг	Arg	Ala 190	Pro	Glu	
	Ile	Met	Leu 195	Asn	Trp	Met	His	Tyr 200	Asn	Gln	Thr	Val	Asp 205	Ile	Trp	Ser	
	Val	Gly 210	_	Ile	Met	Ala	Glu 215	Leu	Leu	Thr	Gly	Arg 220	Thr	Leu	Phe	Pro	
50	Gly 225	Thr	Asp	His	Ile	Asp 230	Gln	Leu	Lys	Leu	Ile 235	Leu	Arg	Leu	Val	Gly 240	
		Pro	Gly	Ala	Glu 245		Leu	Lys	Lys	Ile 250		Ser	Glu	Ser	Ala 255		-
55	Asn	Tyr	Ile	Gln 260		Leu	Thr	Gln	Met 265		Lys	Met	Asn	Phe 270		Asn	
	Val	Phe	Ile	Gly	Ala	Asn	Pro	Leu		Val	Asp	Leu	Leu		Lys	Met	

			275					280					285			
	Leu	Val 290	Leu	Asp	Ser	Asp	Lys 295	Arg	Ile	Thr	Ala	Ala 300	Gln	Ala	Leu	Ala
5	His 305	Ala	Tyr	Phe	Ala	Gln 310	Tyr	His	Asp	Pro	Asp 315	Asp	Glu	Pro	Val	Ala 320
	Asp	Pro	Tyr	Asp	Gln 325	Ser	Phe	Glu	Ser	Arg 330	Asp	Leu	Leu	Ile	Asp 335	Glu
	Trp	Lys	Ser	Leu 340		Tyr	Asp	Glu	Val 345		Ser	Phe	Val	Pro 350	Pro	Pro
10	Leu	Asp	Gln 355		Glu	Met	Glu	Ser 360		Asp	Pro	Pro	Val 365	Ala	Thr	Met
	Val	Ser		Gly	Glu	Glu	Leu 375		Thr	Gly	Val	Val 380	Pro	Ile	Leu	Val
15	Glu 385		Asp	Gly	Asp	Val 390		Gly	His	Lys	Phe		Val	Ser	Gly	Glu 400
		Glu	Gly	Asp	Ala 405		Tyr	Gly	Lys	Leu 410	Thr	Leu	Lys	Phe	Ile 415	Cys
	Thr	Thr	Gly	Lys 420		Pro	Val	Pro	Trp 425		Thr	Leu	Val	Thr 430	Thr	Leu
20	Thr	Tyr	Gly 435	Val	Gln	Cys	Phe	Ser 440	Arg	Tyr	Pro	Asp	His 445	Met	Lys	Gln
	His	Asp 450	Phe	Phe	Lys	Ser	Ala 455	Met	Pro	Glu	Gly	Tyr 460	Val	Gln	Glu	Arg
25	Thr 465	Ile	Phe	Phe	Lys	Asp 470	Asp	Gly	Asn	Tyr	Lys 475	Thr	Arg	Ala	Glu	Val 480
	Lys	Phe	Glu	Gly	Asp 485	Thr	Leu	Val	Asn	Arg 490	Ile	Glu	Leu	Lys	Gly 495	Ile
	Asp	Phe	Lys	Glu 500	Asp	Gly	Asn	Ile	Leu 505	Gly	His	Lys	Leu	Glu 510	Tyr	Asn
30	Tyr	Asn	Ser 515	His	Asn	Val	Tyr	Ile 520	Met	Ala	Asp	Lys	Gln 525	Lys	Asn	Gly
	Ile	Lys 530	Val	Asn	Phe	Lys	Ile 535	Arg	His	Asn	Ile	Glu 540	Asp	Gly	Ser	Val
35	Gln 545	Leu	Ala	Asp	His	Tyr 550	Gln	Gln	Asn	Thr	Pro 555	Ile	Gly	Asp	Gly	Pro 560
	Val	Leu	Leu	Pro	Asp 565	Asn	His	Tyr	Leu	Ser 570	Thr	Gln	Ser	Ala	Leu 575	Ser
	Lys	Asp	Pro	Asn 580	Glu	Lys	Arg	Asp	His 585	Met	Val	Leu	Leu	Glu 590	Phe	Val
40	Thr	Ala	Ala 595	Gly	Ile	Thr	Leu	Gly 600	Met	Asp	Glu	Leu	Tyr 605	Lys		
			(2)) IN	FORM	ATIO	v FO	R SE	Q ID	NO:	66:					
45		(.	i) SI	EOUE	NCE (CHAR	ACTE	RIST	ICS:							
			(A)	LEN	GTH: E: ni	291	3 ba	se p								
			(C)	STR	ANDE	DNES	S: s	ingl	е							
50			(D)	TOP	OLOG'	Y: 1	ınea	r								
			ii) ix)			TYP	E: c	DNA								
55					ME/K				eque	nce						

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

		•	-	-													
5		AGT Ser															~.48
10		AGA Arg															96
15		AAA Lys															144
10		CCT Pro 50															192
20		AGG Arg															240
25		ATC Ile															288
30		GCA Ala													_	_	3,36
25		ACT Thr															384
35		CCT Pro 130															432
40		TGT Cys															480
45		CGA Arg															528
50		GAT Asp															576
55		CCA Pro															624
55	TTA	GCT	CCA	GAA	GTA	CAA	AGC	TCC	GAA	GAA	TAT	TTA	CAG	CTA	TTG	AAG	672

	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	Ile 220	Gln	Leu	Leu	Lys	
5														CTT Leu			720
10														TCC Ser			768
45														CCT Pro 270			816
15														CTC Leu			864
20														CAG Gln			912
25														GCC Ala			960
30														TAC Tyr			1008
35														ACA Thr 350			1056
33														GGT Gly			1104
40														AAA Lys			1152
45														TTC Phe			1200
50														GCT Ala	_		1248
55														AAA Lys 430			1296
J J	CAG	GAT	CAA	GTT	GTC	AAA	GAA	GAT	AAT	ATT	GAA	GCT	GTA	GGG	AAA	AAA	1344

145

										145							
	Gln	Asp	Gln 435	Val	Val	Lys	Glu	Asp 440	Asn	Ile	Glu	Ala	Val 445	Gly	Lys	Lys	
5									CAA Gln								1392
10									ACA Thr								1440
15									GAA Glu								1488
									AGC Ser 505					_		_	1536
20									ATA Ile								1584
25									GAA Glu								1632
30									GCA Ala								1680
35									GAC Asp							_	1728
33									ACT Thr 585								1776
40									GAA Glu								1824
45									CCC Pro								1872
50									AAA Lys								1920
55									CGG Arg								1968
55	TAT	GCC	TGC	TCT	GTA	GTG	GTG	GAC	GGC	GAA	GTA	AAG	CAT	TGT	GTC	ATA	2016

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										140							
	Tyr	Ala	Cys	Ser 660	Val	Val	Val	Asp	Gly 665	Glu	Val	Lys	His	Cys 670	Val	Ile	
5				GCA Ala													2064
10				AAA Lys													2112
45				GAC Asp													2160
15				CGA Arg													2208
20				TTC Phe 740													2256
25				GGC Gly													2304
30				GGC Gly											_		2352
35				CCC Pro													2400
33				AGC Ser													2448
40				ATG Met 820													2496
45				GGC Gly													2544
50				GTG Val												_	2592
55				ATC Ile												_	2640
	AAC	GTC	TAT	ATC	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGC	ATC	AAG	GTG	AAC	2688

										147							
	Asn	Val	Tyr	Ile	Met 885	Ala	Asp	Lys	Gln	Lys 890	Asn	Gly	Ile	Lys	Val 895	Asn	
5										GGC Gly							2736.
10										GAC Asp							2784
4 F										GCC Ala							2832
15										GAG Glu							2880
20						GAC Asp				AAG Lys 970	TAA						2913
25			(2)) INI	FORM	ATIO	N FOI	R SE(Q ID	NO:	57:						
30			(A) (B) (C) (D)	LENG TYPI STRA TOPO	ETH: E: ar ANDEI OLOGI	CHARA 970 mino DNESS Y: 1:	amin acio S: s: inean	no ao i ingle r	cids								
35		(7	/) FI	RAGMI	ENT '	TYPI TYPE DES(: in	cerna	al	Q ID	NO:	57:					-
40	1				5					Ala 10 Leu					15		
40			Gly	20					25	Phe				30			
45		50					55	Leu		Gly		60	Glu				,
	65					70				Val Arg	75					80	
50	-			Gly	85				Glu	90				Gln	95	Ala	
			115					120		Phe			125				
55		130					135					140				Leu	
	Glu	Cys	Ser	Thr	Leu	Tyr	Arg	Thr	Gln	Ser	Ser	Ser	Asn	Leu	Ala	Glu	

	145					150					155					160
	Leu	Arg	Gln	Leu	Leu 165	Asp	Cys	Asp	Thr	Pro 170	Ser	Val	Asp	Leu	Glu 175	Met
5	Ile	Asp	Val	His 180	Val	Leu	Ala	Asp	Ala 185	Phe	Lys	Arg	Tyr	Leu 190	Leu	Asp
			Asn 195					200			-		205			
	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	Ile 220	Gln	Leu	Leu	Lys
10	225		Ile	_		230					235	-	_			240
		-	Leu		245				-	250					255	_
15			Leu	260		_			265					270		
		_	Phe 275					280					285			
		290	Glu				295			_		300				
20	305		Leu			310					315					320
	-		Asn		325					330					335	
25	_		Ser	340					345					350		
			Phe 355					360					365			
		370	Thr				375					380				
30	385	_	Asp	_	_	390	_			_	395	•				400
			Glu		405			_	_	410					415	
35			Lys	420					425					430		
			Gln 435					440					445			
		450	Glu				455					460				
40	465		Tyr			470					475					480
	_		Ala		485					490					495	
45		_	Gln	500				_	505	_				510		
	-	_	Glu 515	_			_	520					525			
		530	Leu				535					540				
50	545		Glu	_		550					555	_	_			560
			Met		565					570					575	
55			Gln	580			_		585					590		
	Lys	Leu	Asn	Glu	Trp	Leu	Glv	Asn	Glu	Asn	Thr	Glu	Asp	GIn	Tyr	ser

			595					600					605			
	Leu	Val		Asp	Asp	Glu	Asp		Pro	His	His	Asp		Lvs	Thr	Trp
		610		-	•		615					620		•		•
	Asn	Val	Gly	Ser	Ser	Asn	Arg	Asn	Lys	Ala	Glu	Asn	Leu	Leu	Arg	Gly
5	625					630					635					640
	Lys	Arg	Asp	Gly	Thr	Phe	Leu	Val	Arg	Glu	Ser	Ser	Lys	Gln	Gly	Cys
					645	_	•_		_	650					655	_
	-		-	660				_	Gly 665			_		670		
10	Asn	Lys	Thr 675	Ala	Thr	Gly	Tyr	Gly 680	Phe	Ala	Glu	Pro	Tyr 685	Asn	Leu	Tyr
	Ser	Ser 690	Leu	Lys	Glu	Leu	Val 695	Leu	His	Tyr	Gln	His 700	Thr	Ser	Leu	Val
		His	Asn	Asp	Ser		Asn	Val	Thr	Leu		Tyr	Pro	Val	Tyr	
15	705	~ 1	3	x	~1	710	D	D	77- 7		715		**- 7	0	7	720
					725	_			Val	730					735	_
	Glu	Glu	Leu	Phe 740	Thr	Gly	Val	Val	Pro 745	Ile	Leu	Val	Glu	150 750	Asp	Gly
20	Asp	Val	Asn 755	Gly	His	Lys	Phe	Ser 760	Val	Ser	Gly	Glu	Gly 765	Glu	Gly	Asp
	Ala	Thr 770	Tyr	Gly	Lys	Leu	Thr 775	Leu	Lys	Phe	Ile	Cys 780	Thr	Thr	Gly	Lys
25	Leu 785	Pro	Val	Pro	Trp	Pro 790	Thr	Leu	Val	Thr	Thr 795	Leu	Thr	Tyr	Gly	Val 800
	Gln	Cys	Phe	Ser	Arg 805	Tyr	Pro	Asp	His	Met 810	Lys	Gln	His	Asp	Phe 815	Phe
	Lys	Ser	Ala	Met 820	Pro	Glu	Gly	Tyr	Val 825	Gln	Glu	Arg	Thr	Ile 830	Phe	Phe
30	Lys	Asp	Asp 835	Gly	Asn	Tyr	Lys	Thr 840	Arg	Ala	Glu	Val	Lys 845	Phe	Glu	Gly
	Asp	Thr 850	Leu	Val	Asn	Arg	Ile 855	Glu	Leu	Lys	Gly	Ile 860	Asp	Phe	Lys	Glu
	Asp	Gly	Asn	Ile	Leu	_	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	
35	865	**. 7		- 1 -		870		T	~ 3	•	875	a 1	~ 7 -	~	77 - T	880
					885				Gln	890					895	
	Phe	Lys	Ile	Arg 900	His	Asn	Ile	Glu	Asp 905	Gly	Ser	Val	Gln	Leu 910	Ala	Asp
40	His	Tyr	Gln 915	Gln	Asn	Thr	Pro	Ile 920	Gly	Asp	Gly	Pro	Val 925	Leu	Leu	Pro
	Asp	Asn 930	His	Tyr	Leu	Ser	Thr 935	Gln	Ser	Ala	Leu	Ser 940	Lys	Asp	Pro	Asn
45	Glu 945	Lys	Arg	Asp	His	Met 950	Val	Leu	Leu	Glu	Phe 955	Val	Thr	Ala	Ala	Gly 960
		Thr	Leu	Gly	Met 965		Glu	Leu	Tyr	Lys 970						
50			(2)	INI	FORM	OITA	1 FOI	R SE	Q ID	NO: 6	58:					
50		(:	i) SI	EQUEI	ICE (CHARA	ACTE	RIST	ICS:			-				
							B bas	_	airs							

149

æ ï

(B) TYPE: nucleic acid(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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150

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

5

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...1785

(D) OTHER INFORMATION:

(xi)	SEQUENCE	DESCRIPTION:	SEO	ID	NO:68:
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	()	(1) 5	EQUE	ENCE	DESC	RIPT	LION:	SEC	מד נ	NO: 6	8:			
10											GAG Glu			48
15	 										CTG Leu			96
20											TTT Phe			144
25											CTG Leu 60			192
10											GAC Asp		_	240
30											GAG Glu			288
35											GAA Glu			336
40											GTA Val		_	384
45											AGC Ser 140			432
43											GAG Glu			480
50											AAT Asn			528
55											TTT Phe			576

5			ACT Thr									624
3			CTG Leu									672
10			CTC Leu									720
15		•	CCT Pro								_	768
20			TCC Ser 260									816
25			GTG Val									864
			ATC Ile								_	912 :
30			CAG Gln									960
35			GAC Asp								_	1008
40			ATC Ile 340	Glu	Lys	Cys	Lys	Glu				1056
45			AGT Ser									1104
			TTA Leu									1152
50			GAA. Glu									_1200
55			ACT Thr									1248

152

		CTC Leu															1296
5																	
		CAG													_	_	1344
	Lys	Gln		Asp	Phe	Phe	Lys		Ala	Met	Pro	Glu	-	Tyr	Val	Gln	
			435					440					445				
10	~ n n	707	» cm	א מיים	mmm	ma c	***	C N TT	CAC	ccc	770	TO C	7 7 C	א כי א	CCT	CCT	1392
10		AGA Arg														_	1332
	GIU	450	1111	116	FIIC	I Y I	455	vab	тэр	Gry	A311	460	цуз	1111	A-9	ALU	
		150															
	GAA	GTC	AAG	TTT	GAA	GGT	GAT	ACC	CTT	GTT	AAT	AGA	ATC	GAG	TTA	AAA	1440
15	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	
	465					470					475					480	
		ATT															1488
20	Gly	Ile	Asp	Phe	•	Glu	Asp	GIY	Asn		Leu	GIA	His	гуѕ		GIU	
20					485					490					495		
	тас	AAT	ידעיד	ממ	тса	САТ	таа	СΤЪ	ТАС	АТС	ATG	GCA	GAC	ΔΔΔ	CCA	AAG	1536
		Asn															
	-1-		-1-	500					505				-	510		-	
25																	
	AAT	GGC	ATC	AAA	GTT	AAC	TTC	AAA	ATT	AGÀ	CAC	AAC	ATT	AAA	GAT	GGA	1584
	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Lys	Asp	Gly	
			515					520					525				
20	3.00	amm.	CI N N	mm x	GG3	a n a	C N TT	m v m	<i></i>	~ n n	חתת	3 CT	CCA	אתיתי	CCC	CAT	1632
30		GTT Val												_	_		1032
	ser	530	GIII	beu	ALA	АЗР	535	TYL	GIII	GIII	ASII	540	FIO	110	Ory	Aob	
		330					-					313					
	GGC	CCT	GTC	CTT	TTA	CCA	GAC	AAC	CAT	TAC	CTG	TCC	ACG	CAA	TCT	GCC	1680
35	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	
	545					550					555					560	
		TCC														_	1728
40	Leu	Ser	гÀг	Asp		Asn	GIU	гàг	Arg	-	His	Met	ııe	Leu	ьеи 575	GIU	
40					565					570					ر, ر		
	TTT	GTA	ACA	GCT	GCT	GGG	ATT	ACA	CAT	GGC	ATG	GAT	GAA	CTA	TAC	AAA	1776
		Val								_							
				580		•			585	4		•		590	-	=	
45																	
		CAG	-	TAA													1788
	Pro	Gln															
			595														
50																	
50			(2) TN	FORM	יחדיים	N FO	R SE	מד מ	NO ·	69·						
			, -	,													
						~											

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 595 amino acids
- (B) TYPE: amino acid
 - (C) STRANDEDNESS: single

153

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

	Met 1	Gly	Asn	Ala	Ala 5	Ala	Ala	Lys	Lys	Gly 10	Ser	Glu	Gln	Glu	Ser 15	Val
10	Lys	Glu	Phe	Leu 20	Ala	Lys	Ala	Lys	Glu 25	Asp	Phe	Leu	Lys	Lys 30	Trp	Glu
	Asp	Pro	Ser 35	Gln	Asn	Thr	Ala	Gln 40	Leu	Asp	Gln	Phe	Asp 45	Arg	Ile	Lys
15	Thr	Leu 50	Gly	Thr	Gly	Ser	Phe 55	Gly	Arg	Val	Met	Leu 60	Val	Lys	His	Lys
	Glu 65	Ser	Gly	Asn	His	Tyr 70	Ala	Met	Lys	Ile	Leu 75	Asp	Lys	Gln	Lys	Val 80
	Val	Lys	Leu	Lys	Gln 85	Ile	Glu	His	Thr	Leu 90	Asn	Glu	Lys	Arg	Ile 95 ·	
20	Gln	Ala	Val	Asn 100	Phe	Pro	Phe	Leu	Val 105	Lys	Leu	Glu	Phe	Ser 110	Phe	Lys
	Asp	Asn	Ser 115	Asn	Leu	Tyr	Met	Val 120	Met	Glu	Tyr	Val	Ala 125	Gly	Gly	Glu
25	Met	Phe 130	Ser	His	Leu	Arg	Arg 135	Ile	Gly	Arg	Phe	Ser 140	Glu	Pro	His	Ala
	Arg 145	Phe	Tyr	Ala	Ala	Gln 150	Ile	Val	Leu	Thr	Phe 155	Glu	Tyr	Leu	His	Ser 160
	Leu	Asp	Leu	Ile	Tyr 165	Arg	Asp	Leu	Lys	Pro 170	Glu	Asn	Leu	Leu	Ile 175	Asp
30	Gln	Gln	Gly	Tyr 180	Ile	Gln	Val	Thr	Asp 185	Phe	Gly	Phe	Ala	Lys 190	Arg	Val
	Lys	Gly	Arg 195	Thr	Trp	Thr	Leu	Cys 200	Gly	Thr	Pro	Glu	Tyr 205	Leu	Ala	Pro
35		210				-	215	_		_		220			Trp	
	225	_				230					235				Phe	240
	Ala	Asp	Gln	Pro	Ile 245	Gln	Ile	Tyr	Glu	Lys 250	Ile	Val	Ser	Gly	Lys 255	Val
40	_			260					265					270	Arg	
			275					280					285		qaA	
45		290					295					300			Trp	
	305					310					315				Phe	320
	-		_	_	325					330					Glu 335	
50				340			_		345					350	Phe	
			355		_	-		360					365		Pro	
55	Leu	Val 370	Glu	Leu	Asp	Gly	Asp 375	Val	Asn	Gly	Gln	Lys 380	Phe	Ser	Val	Ser
	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe

	385					390					395					400	
	Ile	Cys	Thr	Thr	Gly 405	Lys	Leu	Pro	Val	Pro 410	Trp	Pro	Thr	Leu	Val 415	Thr	
5	Thr	Leu	Thr	Tyr 420	Gly	Val	Gln	Cys	Phe 425	Ser	Arg	Tyr	Pro	Asp 430	His	Met	
	Lys	Gln	His 435	Asp	Phe	Phe	Lys	Ser 440	Ala	Met	Pro	Glu	Gly 445	Tyr	Val	Gln	
	Glu	Arg 450	Thr	Ile	Phe	Tyr	Lys 455	Asp	Asp	Gly	Asn	Tyr 460	Lys	Thr	Arg	Ala	
10	Glu 465	Val	Lys	Phe	Glu	Gly 470	Asp	Thr	Leu	Val	Asn 475	Arg	Ile	Glu	Leu	Lys 480	
	Gly	Ile	Asp	Phe	Lys 485	Glu	Asp	Gly	Asn	Ile 490	Leu	Gly	His	Lys	Met 495	Glu	
15	Tyr	Asn	Tyr	Asn 500	Ser	His	Asn	Val	Tyr 505	Ile	Met	Ala	Asp	Lys 510	Pro	Lys	
	Asn	Gly	Ile 515	Lys	Val	Asn	Phe	Lys 520	Ile	Arg	His	Asn	Ile 525	Lys	Asp	Gly	
	Ser	Val 530	Gln	Leu	Ala	Asp	His 535	Tyr	Gln	Gln	Asn	Thr 540	Pro	Ile	Gly	Asp	
20	Gly 545	Pro	Val	Leu	Leu	Pro 550	Asp	Asn	His	Tyr	Leu 555	Ser	Thr	Gln	Ser	Ala 560	
		Ser	Lys	Asp	Pro 565		Glu	Lys	Arg	Asp 570		Met	Ile	Leu	Leu 575	Glu	
25	Phe	Val	Thr	Ala 580		Gly	Ile	Thr	His 585		Met	Asp	Glu	Leu 590		Lys	
	Pro	Gln	Glu 595														
				INI	FORM	OITA	ı FOI	R SE	O ID	NO:	70:						
30		(:			ICE (
			(A)	LENG	STH: S: nu	218	l bas	se pa									
35			(C)	STRA	ANDEI	ONES	3: s:	ingle	=								
		(:	Li) N	40LE0	CULE	TYPI	E: cI	ONA									
			ix) I														
40					ME/KI				eque	nce							
			(D)	OTI	HER :	INFO	RMAT	ON:									
45		()	ci) S	SEQUI	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	70:					
		AGC Ser															48
	1				5			-1-		10				-,-	15	1	
50		TAC Tyr															96
		- 2 -		20	-:-	- ₽	3		25	- 3 -				30			
55		ACC Thr															144
	4		35		1	4	4	40	3				45		-		

5			AAC Asn							192
3	 	 	CGG Arg							240
10			GAA Glu 85							288
15			ACC Thr							336
20	 _		GAG Glu							384
25			GAG Glu							432
23			GAG Glu					_	_	480
30			ATC Ile 165							528
35			CTC Leu							57 <u>6</u>
40			ACC Thr							624
45			CTG Leu							672
.0			TAC Tyr							720
50			TTC Phe 245							768
55			CTG Leu							816

5			CTG Leu										864
3			TTC Phe								_	_	912
10			TTT Phe										960
15			GAC Asp 325							_		_	1008
20			GAG Glu										1056
25	 	 	CTT Leu										1104
20			GGT Gly										1152
30			AAG Lys										1200
35			CAT His 405									_	1248
40	Glu	Lys	CTC Leu		Pro	Lys	Pro	Gln	Val				1296
45			TAT Tyr										1344
40			GAC Asp										1392
50			TTC Phe										1440
55			GTC Val 485				Lys						1488

. 157

	GGG Gly												1	.536
5	 AAG Lys												1	.584 -
10	CTG Leu 530												1	.632
15	CCC Pro												1	.680
20	TAC Tyr												1	.728
25	GAA Glu												1	776
	TAC Tyr													
30	CGC Arg 610											ATC Ile	1	L872
35	GGG Gly]	L920
40	GCC Ala	Asp	Gln	Lys	Asn	Gly	Ile	Lys	Val		_		. 1	1968
45	AAC Asn												2	2016
	ACC Thr												2	2064
50	AGC Ser 690												1	2112
55					Phe							GGC Gly 720	:	2160

158

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ATG GAC GAG CTG TAC AAG TAA
                                                                          2181
      Met Asp Glu Leu Tyr Lys
                      725
5
               (2) INFORMATION FOR SEQ ID NO:71:
            (i) SEQUENCE CHARACTERISTICS:
10
              (A) LENGTH: 726 amino acids
              (B) TYPE: amino acid
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
15
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:
20
     Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly
      Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp
                                     25
      Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg
25
                                 40
      Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys
      Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp
30
      Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg
                                         90
      Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys
                                     105
      Gln Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn
35
                                 120
      Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg
                             135
                                                 140
      Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Gly Lys Gly Thr
                                             155
40
      Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr
                                          170
      Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val
                                     185
      Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro
45
                                 200
      Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys
                             215
                                                  220
      Phe Val Met Glu Tyr Ala Asn Gly Glu Leu Phe Phe His Leu Ser
                         230
                                             235
50
      Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu
                     245
                                         250
      Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr
                                     265
      Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile
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Caracher Service Control of the Service Contr

275 280 285 Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala

		290					295					300				
	Thr		Lare	Thr	Dha	Cve		Thr	Pro	Glu	Tur		λΙэ	Dro	Glu	1751
	305	Mec	цуs	1111	FIIC	310	Gry	TIIT	PIO	GIU	315	Leu	міа	PIO	Giu	320
		Gl.	λαπ	λαη	λαη		Gl ₁₄	۸	Ala	17-1		Two	T	~1	τ	
5	пец	Giu	Asp	ASII	325	TAT	Gry	Arg	Ala	330	Asp	пр	пр	GIÀ	335	GIĀ
3	Val	V-1	Mot	Tur		Met	Mot	Cvc	Gly		T ON	Dro	Dho	Т		Cl n
	vai	VAI	Mec	340	Giu	Mec	Mec	Cys	345	Arg	neu	PIO	Pile	350	ASII	GIII
	Λcn	uic	Glu		Lau	Dha	C1.,	Ton		T 011	Mot	~1	~1		7 ~~	Dho
	Asp	HIS	355	пуъ	цец	FIIE	Giu		Ile	Leu	Mec	GIU	365	116	Arg	Pile
10	Dece	7		T 0	01	Dwa	01	360	Lys	.		7		a1	T	T
10	PIO	370	IIII	ьeu	Gry	PIO	375	Ald	ьys	Ser	Leu		ser	GIÀ	Leu	Leu
	Tire		7 an	Dro	Lva	Cln		Ι ου	Gly	01	G1	380	~1. ,	7 ~~	ח ז ה	T
	385	Буб	ASP	FIO	шуз	390	Arg	пеп	GIY	Gry	395	ser	Gru	MSP	MIA	-
		т 1 о	Mot	Cln	uic		Dho	Dha	77.	a 1		17-1	Two	C1 =	111.0	400
15	GIU	116	MEC	GIII	405	Arg	Pile	Pile	Ala	410	116	vaı	пр	GIII	415	vai
13	Tree	C1.,	Lva	Tarc		202	Dro	Dro	Dho		Drea	C1 =	1121	mh		C1. ,
	TYL	GIU	пуъ	420	пеп	361	PIO	PIO	Phe 425	гуу	PLO	GIII	Val	430	Ser	GIU
	Thr	λεπ	Thr		Tur	Dho) cn	C1.,	Glu	Dho	Th.∽	ח ז ח	C1 n		Tla	Thr
	1111	Asb	435	Arg	1 y L	FIIC	чэр	440	Giu	FIIE	1111	Ата	445	Mec	116	IIII
20	Tla	Thr		Dro	λen	Gln	λαη		Ser	Mot	Clu	Crrc		λαν	Car	Clu
20	116	450	FIU	FIU	ASP	GIII	455	Asp	261	MEC	GIU	460	val	Asp	261	Giu
	Ara		Dro	Wie	Dhe	Pro		Dhe	Ser	Tur	Car		Car	Car	Thr	λla
	465	nr 9	FLO	1113	F 11C	470	GIII	FIIC	261	ıyı	475	Ата	261	261	1111	480
		Δen	Pro	Pro	Val		Thr	Met	Val	Sar		Glv	Glu	Glu	Len	
25	001	Пор	110		485	,,,,,	1111		vai	490	Ly 3	Cry	014	Olu	495	1110
	Thr	Glv	Val	Val		Tle	Leu	Va 1	Glu		Δsn	Glv	Asn	Val		Glv
		O L J		500	110			• • • •	505	пси	App	Cry	nop	510	71011	Q L y
	His	Lvs	Phe		Val	Ser	Glv	Glu	Gly	Glu	Glv	Asn	Δla		Tvr	Glv
		_, _	515			552	U -1	520	0+7	- Lu	Cry	11.55	525		-1-	
30	Lvs	Leu		Leu	Lvs	Phe	Tle		Thr	Thr	Glv	Lvs		Pro	Val	Pro
	-,-	530			-1 -		535	-1-				540				
	Trp		Thr	Leu	Val	Thr		Leu	Thr	Tvr	Glv		Gln	Cvs	Phe	Ser
	545					550				- 1 -	555			-1-		560
	Arg	Tvr	Pro	asA	His		Lvs	Gln	His	Asp		Phe	Lvs	Ser	Ala	
35	3	- 1 -			565		-1 -			570			-1-		575	
	Pro	Glu	Glv	Tyr	Val	Gln	Glu	Ara	Thr		Phe	Phe	Lvs	Asp	Asp	Glv
			_	580				5	585				-	590		1
	Asn	Tvr	Lvs		Arq	Ala	Glu	Val	Lys	Phe	Glu	Glv			Leu	Val
		-	595					600	-				605			
40	Asn	Arg	Ile	Glu	Leu	Lys	Gly		Asp	Phe	Lvs	Glu		Glv	Asn	Ile
		610					615				-1 -	620		1		
	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile
	625	-		-		630	•		-		635				•	640
	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	
45			_	•	645	-		•		650				-	655	_
	His	Asn	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln
				660	-	-			665			-		670		
	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr
			675		_	_	-	680					685			-
50	Leu	Ser	Thr	Gln	Ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp
		690					695		-	-		700		-	_	-
	His	Met	Val	Leu	Leu	Glu	Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly
	705					710					715					720
	Met	Asp	Glu	Leu	Tyr	Lys										
55					725											

		(2)	INI	ORMA	ATION	1 FOF	SEC] ID	NO:7	72:					
5	(i	(A) (B) (C)	LENC TYPE	ETH: E: nu ANDEI	2751 iclei ONESS	bas c ac	ngle	irs							
10			OLEC FEATU		TYPE	E: cI	ANO								
15		(B)	NAM LOC	CATIC)N:]	ι2		equer	ıce						
	()	ci) S	EQUI	ENCE	DESC	CRIPT	CION:	SEC) ID	NO: 7	72:				
20	 							-	TCC Ser 10		_				48
25									CTG Leu						96
25									CGC Arg						144
30									TGG Trp						192
35									GTT Val						240
40	 								GAT Asp 90		-	-			288
									ATC Ile						336
45									CTC Leu				_	_	384
50									AAT Asn						432
55									GAT Asp						480

5							AAG Lys		_	_	528
ŭ							CCA Pro				576
10							CCC Pro				624
15							AAT Asn 220	_			672
20							AAA Lys				720
25							CGG Arg				768
							AAG Lys		_		816
30							GAA Glu				864
35							GAA Glu 300				912
40							AAA Lys				960
45							GAC Asp				1008
40							GGG Gly				1056
50							CTG Leu				1104
55						Asp	GAC Asp 380				1152

5		GTG Val									1200
3		CAG Gln									1248
10		GAA Glu									1296
15		AAA Lys									1344
20		GGA Gly 450									1392
25		CTG Leu									1440
		TTC Phe									1488
30		TTC Phe									1536
35		CCG Pro									1584
40	Tyr	GAG Glu 530		Ala	Gln	Pro	Phe	Asp	Glu	_	1632
45		CTG Leu									1680
.0		TCC Ser									1728
50		GCC Ala									1776
55		CAT His									1824

5		 								GGA Gly		1872
J										ACA Thr		1920
10										GAA Glu		1968
15										AGT Ser 670		2016
20										GTT Val		2064
25										TTC Phe		2112
										ACC Thr		2160
30										ACG Thr		2,208
35										CCA Pro 750		2256
40	Met	Gln	His	Asp	Phe	Phe	Ser			Gly	GTA Val	2304
45										AAG Lys		2352
										ATC Ile	TTA Leu 800	2400
50										CAC His		2448
55										GAC Asp 830	CCA Pro	2496

												~ . ~				G. N. M.	2544
		AAT Asn															2544
5	221	200	amm	G. D. D.	mm a	001	a.a.	03 m		a	<i>~</i>			GG3	3 CC	aaa	2502
		AGC Ser					Asp					Asn					2592
		850					855					860					
10		GGC						_			_						2640
	865	Gly	Pro	Val	Leu	Leu 870	Pro	Asp	Asn	His	Tyr 875	Leu	Ser	Thr	Gln	Ser 880	
		CTT	TCC	ΔΔΔ	GAT		ממ	GAA	ΔAG	ΔGΔ		CAC	ΔΤС	ልጥሮ	ርጥጥ	СТТ	2688
15		Leu															2000
					885					890					895		
	GAG	TTT	GTA	ACA	GCT	GCT	GGG	ATT	ACA	CAT	GGC	ATG	GAT	GAA	CTA	TAC	2736
20	Glu	Phe	Val	Thr 900	Ala	Ala	Gly	Ile	Thr 905	His	Gly	Met	Asp	Glu 910	Leu	Tyr	
20				500					903					910			
		CCT Pro			TAA												2751
	цуъ	FIO	915	Giu													
25																	
			(2)	INI	ORMA	OITA	1 FOI	R SE	Q ID	ΝО:	73:						
		7 -	: \ CT	EQUE	ice (~U 7 D 7	CTT	י ד כי מי	rce.								
30		(-	-	LENG													
				TYPI					_								
				STRA TOPO				_	3							•	
25				101 F/	3117 E	muni	.										
35				(OLE) RAGMI			_										
		(,	.i\ (e te Oi II	entere	DEC	ים ד סי	PT ON	. 050	` TD	NO . T	73.					
•											NO:						
40	Met 1	Ala	Asp	Val	Tyr 5	Pro	Ala	Asn	Asp	Ser 10	Thr	Ala	Ser	Gln	Asp 15	Val	
	Ala	Asn	Arg		Ala	Arg	Lys	Gly		Leu	Arg	Gln	Lys		Val	His	
	Glu	Val	Lys	20 Asp	His	Lys	Phe	Ile	25 Ala	Arg	Phe	Phe	Lys	30 Gln	Pro	Thr	
45			35	-		•				_			_				
		_	_	1			_	40		_			45	_		~ 1	
	Phe	Cys 50	Ser	His	Cys	Thr	Asp 55		Ile	Trp	Gly	Phe 60		Lys	Gln	Gly	
	Phe	_			_	Cys	55	Phe		_	His	60	Gly			Glu	
50	Phe 65	50 Gln	Cys	Gln	Val	Cys 70	55 Cys	Phe Phe	Val	Val	His	60 Lys	Gly Arg	Cys	His	Glu 80	
50	Phe 65 Phe	50 Gln Val	Cys Thr	Gln Phe	Val Ser 85	Cys 70 Cys	55 Cys Pro	Phe Phe Gly	Val Ala	Val Asp 90	His 75 Lys	60 Lys Gly	Gly Arg Pro	Cys Asp	His Thr 95	Glu 80 Asp	
50	Phe 65 Phe	50 Gln	Cys Thr	Gln Phe Ser	Val Ser 85	Cys 70 Cys	55 Cys Pro	Phe Phe Gly	Val Ala Lys	Val Asp 90	His 75 Lys	60 Lys Gly	Gly Arg Pro	Cys Asp Gly	His Thr 95	Glu 80 Asp	
50 55	Phe 65 Phe Asp	50 Gln Val	Cys Thr Arg	Gln Phe Ser 100	Val Ser 85 Lys	Cys 70 Cys His	55 Cys Pro Lys	Phe Phe Gly Phe	Val Ala Lys 105	Val Asp 90 Ile	His 75 Lys His	60 Lys Gly Thr	Gly Arg Pro Tyr	Cys Asp Gly 110	His Thr 95 Ser	Glu 80 Asp Pro	

		130					135					140				
	Ile		Asp	Pro	Ser	Leu		Gly	Met	Asp	His		Glu	Lys	Arq	Gly
	145					150	-	•		•	155			-	_	160
5	Arg	Ile	Tyr	Leu	Lys 165	Ala	Glu	Val	Thr	Asp 170	Glu	Lys	Leu	His	Val 175	Thr
_	Val	Arg	Asp	Ala 180	Lys	Asn	Leu	Ile	Pro 185	Met	Asp	Pro	Asn	Gly 190	Leu	Ser
	Asp	Pro	Tyr 195	Val	Lys	Leu	Lys	Leu 200	Ile	Pro	Asp	Pro	Lys 205	Asn	Glu	Ser
10	Lys	Gln 210	Lys	Thr	Lys	Thr	Ile 215	Arg	Ser	Asn	Leu	Asn 220	Pro	Gln	Trp	Asn
	Glu 225	Ser	Phe	Thr	Phe	Lys 230	Leu	Lys	Pro	Ser	Asp 235	Lys	Asp	Arg	Arg	Leu 240
15	Ser	Val	Glu	Ile	Trp 245	Asp	Trp	Asp	Arg	Thr 250		Arg	Asn	Asp	Phe 255	Met
	-			260		_		Ser	265					270		
	_	-	275					Gln 280					285			
20		290					295	Glu				300				
	305		-			310		Pro			315					320
25			_		325			Ser		330					335	
				340				Val Gly	345					350		
30			355		-			360 Ile					365			
30		370	-	-	_		375	Ala				380				
	385			-	_	390		Gln			395					400
35					405					410					415	Val
			_	420				Ala	425					430		
40	-	-	435	•				440					445			Leu
		450					455					460				Ala
	465					470		His			475					480
45	_		_		485			Tyr		490					495	
				500					505					510		Leu
50			515					520 Pro					525			
		530		*			535					540				Ser
	545	-				550					555				Lys	560 Gln
55					565					570					575	Arg

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				580					585					590		
	Glu	His	Ala 595	Phe	Phe	Arg	Arg	Ile 600		Trp	Glu	Lys	Leu 605	Glu	Asn	Arg
5	Glu	Ile 610	Gln	Pro	Pro	Phe	Lys 615	Pro	Lys	Val	Cys	Gly 620	Lys	Gly	Ala	Glu
	Asn 625	Phe	Asp	Lys	Phe	Phe 630	Thr	Arg	Gly	Gln	Pro 635	Val	Leu	Thr	Pro	Pro 640
	Asp	Gln	Leu	Val	Ile 645	Ala	Asn	Ile	Asp	Gln 650	Ser	Asp	Phe	Glu	Gly 655	Phe
10		Tyr		660					665					670		
	-	Arg	675			_		680					685			
15		Leu 690					695	_			_	700				
	705	Gly		_		710				_	715					720
20		Ile	_		725		_			730					735	
20		Thr		740	_	_			745					750		
		Lys	755		-			760					765			
25		Glu 770					775					780				
	785	Glu		_		790	_	-			795		_			800
20	_	Gly			805			_	_	810					815	
30		Tyr		820					825					830		
	_	Asn	835					840					845			
35	_	Ser 850					855		•			860				
	865	Gly				870		-			875					880
40		Leu Phe		-	885				-	890	_				895	
40		Pro		900	AIG	Ala	Gly	116	905	nis	G1.y	Mec	Asp	910	Deu	. y .
	-2-		915													
45			(2) IN	FORM	ATIO	N FO	R SE	Q ID	ио:	74:					
		(i) S: (A)	EQUE:												
50			(C)	TYP:	ANDE	DNES	S: s	ingl	e							
				TOP												
			ii) ix)			TYP:	E: C	ANU								
55					/		a	_								

(A) NAME/KEY: Coding Sequence

167

(B) LOCATION: 1...2154(D) OTHER INFORMATION:

5			()	(i) S	EQUE	ENCE	DESC	CRIPT	ION:	SEC) ID	ΝΟ : 7	74:						ა .
Met Ser Ser Ile Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu Leu 15	5																		
1																			48
Gly Trp Lys Lys Ser Ala Gly Gly Ser Gly Gly Ala Gly Gly Gly Glu 20 25 30 310			261	Ser	116		FIO	FIIC	1111	FIU		vai	Vai	Бүз	AL 9		пси		
Gly Trp Lys Lys Ser Ala Gly Gly Ser Gly Gly Ala Gly Gly Gly Glu 20 25 30 310																			
20	10																		96
15 Gln Asn Gly Gln Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu GTG AAG AAG CTA AAG AAA ACA GGA CGA TTA GAT GAG CTT GAG AAA GCC Val Lys Lys Leu Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala 20 50 50 55 5 5 6 60 60 60 60 60 60 60 60 60 60 60 60 6		GIY	пр	пуз	_	561	AIG	Gry	Gry		Gry	Gry	AIG	Gry		Cly	O1 a		
15 Gln Asn Gly Gln Glu Glu Lys Trp Cys Glu Lys Ala Val Lys Ser Leu 35 AAG AAG CTA AAG AAA ACA GGA CGA TTA GAT GAG CTT GAG AAA GCC Val Lys Lys Leu Lys Lys Thr Gly Arg Leu Asp Glu Leu Glu Lys Ala 20 50 Ser Gln Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr 65 70 70 75 TGC TCT GAA ATT TGG GGA CTG AGT ACA ACA CCA AAT ACA AST THR Ile Pro Ser Thr 80 Cys Ser Glu Ile Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp 85 Gln Trp 90 Asn Thr Arg Ser Leu Asp Gln Trp 95 Ser Leu Asp 110 Trp 95 Ser Leu Asp 110 Trp 95 Ser Leu Asp 110 Ser His Arg Lys Gly Leu Pro His Val Ile Tyr 115 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CCA AGT CAT ACA AGG ATT ATA TAT TAT 115 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT GAT CTT ATA TAT 116 Tyr 117 Trp 118 Trp 119 Trp 110 Trp 115 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG AGA ACC AGG TGT TTA TGG CGC TGG CTT ATA TAT TAT 118 Trp 120 TGC CGA TTA TGG CGC TGG CTT ATA TAT TAT TAT 1384 45 TGT GTA AAC CCT TAC CAG TTA TGT ATA TAT GTT ATA TAT TAT 1364 145 TGT GTA AAC CCT TAC CAC TAT CAC AGG TTT TAT AAT CTT AAA AAG GAT GAA CTC AAG AGA ATT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA CTC AAG Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGG TTT TAT TAT TAT TAT 150 TGT GTA AAC CTT TAC CAC TAT CAG AGG TTT TAT TAT TAT TAT TAT 160 TGT GTA AAC CTT TAC CAC TAT CAG AGG TTT TAT TAT TAT TAT TAT TAT TAT T																			
ST ST ST ST ST ST ST ST	15																		144
Val	15	GIII	ASII	_	GIII	Giu	Giu	цуз		Cys	Giu	БУБ	AIG		шуз	DCI	DCu		
Val																			
20																	_		192
ATC ACC ACT CAA AAC TGT AAT ACT AAA TGT GT AAT ACT ACT ACT ACT ACT ACT GT ACT ACT ACT ACT ACT ACT ACT ACT ACT AC	20	vai	-	цуѕ	ьец	цуз	Буб		Gly	AIG	пец	Asp		Deu	Giu	шуз	AIG		
The Thr Thr Gln Asn Cys Asn Thr Lys Cys Val Thr Ile Pro Ser Thr 80																			
TGC																		•	240
25 TGC TCT GAA ATT TGG GGA CTG AGT ACA CCA AAT ACG ATA GAT CAG TGG Cys Ser Glu Ile Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp 95 30 GAT ACA ACA GGC CTT TAC AGC TTC Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp 110 GGT CGT CTC CAG GTA TCC CAT CAT CAT AAG AGA ACA ACA ACC ATG TAT TAT 115 GGY Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr 125 TGC CGA TTA TGG CGC TGG CCT GAT CTT AAA ACG AGT CAT CAT GAA CTC AAG CYs Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 140 GCA ATT GAA AAC TGC GAA TAT GCT TTT AAA AAG GAT GAA GGA GTA AAG ACC CYs AAG ACC CYs AAG ACC CYs CYs Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 140 GCA ATT GAA AAC CCT TAC CAC TAT CAG AGA GTT TTT AAT CTT AAA AAG GAT GAA GTA AAG ACC CYs AA			1111	1111	GIII	ASII		ASII	1.111	пуз	Cys		TILL	116	FIO	Der			
Cys Ser Glu Ile Trp Gly Leu Ser Thr Pro Asn Thr Ile Asp Gln Trp 95 30 GAT ACA ACA GGC CTT TAC AGC TTC TCT GAA CAA ACC AGG TCT CTT GAT Asp Thr Thr Gly Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp 100 GGT CGT CTC CAG GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT TAT 11s Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr 125 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG CYs Arg Leu Trp Arg Trp Pro Asp Leu His Ser His Ser His Glu Leu Lys 140 GCA ATT GAA AAC TGC GAA TAT GCT TTT AAT CAT TAT TAT TAT TAT TAT TAT T	25																		
30 GAT ACA ACA GGC CTT TAC AGC TTC TCT GAA ACA ACC AGG TCT CTT GAT 336 Asp Thr Thr Gly Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp 35 GGT CGT CTC CAG GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT 384 35 Gly Arg Leu TgG CGC TGG CCT GAT CTT CAC AGT CAT CAT CAT CAT CAT CAT TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG 432 CYS Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 40 GCA ATT GAA AAC TGC GAT TTT AAT TTT AAT TTT AAT TAT AAT Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT Cys Val Asn Pro Tyr His Tyr Gln Arg CTT GAG ACA CCA GTT TTG CCT TGT GTA AAC CCT Tac CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT TTG GTA AAC CCT Tac Tyr Tyr Gln Arg CTT GAG ACA CCA GTT TTG CCT TTG GTA AAC CTT TYr Tyr Tyr Gln Arg CTT TYr Ty																			288
Asp Thr Thr Gly Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp 110 GGT CGT CTC CAG GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT 384 Gly Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr 125 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His Glu Leu Lys 130		Cys	ser	GIU	TTE	_	GIY	ьeu	ser	IIIL		ASII	TIIL	116	Азр		тър		
Asp Thr Thr Gly Leu Tyr Ser Phe Ser Glu Gln Thr Arg Ser Leu Asp 110 GGT CGT CTC CAG GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT 384 Gly Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr 125 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His Glu Leu Lys 130																			
GGT CGT CTC CAG GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT 384 35 Gly Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr 115 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT GAA CTC AAG Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 135 GCA ATT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 175	30																		336
35 GGT CGT CTC CAG GTA TCC CAT CGA AAA GGA TTG CCA CAT GTT ATA TAT 184 Arg Lys Gly Leu Pro His Val Ile Tyr 125 TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG CYs Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 130 GCA ATT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT S28 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT S28 Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 175		Asp	Int	Int	_	Leu	ıyı	ser	Pile		GIU	GIII	TIIL	Arg		пец	ASP		
35 Gly Arg Leu Gln Val Ser His Arg Lys Gly Leu Pro His Val Ile Tyr 115 CGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT GAA CTC AAG Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 130 CGC GAA TAT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165 Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 175 CTT TTG CCT 175																			•
TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG CYS Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 135 GCA ATT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT 528 Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165	25																		384
TGC CGA TTA TGG CGC TGG CCT GAT CTT CAC AGT CAT CAT GAA CTC AAG CYS Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 130	35	GIY	Arg		GIN	vai	ser	HIS		гув	GIA	Leu	PIO		vaı	116	TAT		
Cys Arg Leu Trp Arg Trp Pro Asp Leu His Ser His His Glu Leu Lys 130																			
40 130 135 140 GCA ATT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 150 155 160 45 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165 170 170 175																			432
GCA ATT GAA AAC TGC GAA TAT GCT TTT AAT CTT AAA AAG GAT GAA GTA Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165 170 175 480 480 480 480 480 480 480 48	40	Cys	_	Leu	тгр	AIG	пр		Asp	ren	UIS	Ser		птъ	Giu	neu	цуз		
Ala Ile Glu Asn Cys Glu Tyr Ala Phe Asn Leu Lys Lys Asp Glu Val 145 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165																			
145 150 155 160 45 TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT 528 Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165 170 175																	_		480
TGT GTA AAC CCT TAC CAC TAT CAG AGA GTT GAG ACA CCA GTT TTG CCT 528 Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165 170 175			rre	GIU	ASI	Cys		Tyr	Ala	Pne	ASI		rys	гуѕ	Asp	GIU			
Cys Val Asn Pro Tyr His Tyr Gln Arg Val Glu Thr Pro Val Leu Pro 165 170 175	45																		
165 170 175																			528
		Cys	vai	ASI	PIO	_	HIS	TYE	GIII	Arg		Gru	1111	PIO	val		PIO		
50 CCA GTA TTA GTG CCC CGA CAC ACC GAG ATC CTA ACA GAA CTT CCG CCT 576																			
	50																		576
Pro Val Leu Val Pro Arg His Thr Glu Ile Leu Thr Glu Leu Pro Pro 180 185 190		Pro	vaı	ьeu		PEO	Arg	uis	THE		тте	neu	THE	GIU		FIO	FIO		
CTG GAT GAC TAT ACT CAC TCC ATT CCA GAA AAC ACT AAC TTC CCA GCA 624 55 Leu Asp Asp Tyr Thr His Ser Ile Pro Glu Asn Thr Asn Phe Pro Ala	55																		624
195 200 205	JJ	.ueu	мър		TYL	TIIL	urs	261		FIO	GIU	L911	1111		FIIG	FIU	ATG		

5							ACG Thr 220				672
_							CAG Gln				720
10							ACT Thr				768
15							TAC Tyr				816
20							CAG Gln			_	864
25							GAT Asp 300				912
			 	 			CTC Leu		_		960
30							ATA ·Ile			_	1008
35							GAG Glu				1056
40							CAG Gln		_		1104
45							TGT Cys 380				1152
	_			 	 	 	CAG Gln				1200
50							TGC Cys				1248
55							AGG Arg			_	1296

E			TGC Cys													1344
5			GTA Val													1392
10			TGG Trp													1440
15			GGC Gly												_	1488
20			GGC Gly 500											_	_	1536
25			GAT Asp													1584
			AAG Lys													1632
30			GTG Val												_	1680
35			TTC Phe													172.8
40		Phe	TTC Phe 580	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala		_	1776
45			GGC Gly													1824
			GAG Glu													1872
50			CAC His													1920
55			AAC Asn												_	1968

5				GAC Asp 660													2016
3				CCC Pro													2064
10				AAC Asn													2112
15				GGG Gly											TAA		2157
20		(:		INI EQUE1					_	NO: 7	75 :						
25			(B)	LENG TYPE STRA	E: an	nino ONESS	acio S: si	i ingle									
20			ii) N	MOLE (CULE	TYPE	E: pi	rotei									
30		()	ki) S	SEQU	ENCE	DESC	CRIP	NOIT	SE	DI C	NO: 7	75:					
30	Met 1			EEQUI									Lys	Arg	Leu 15	Leu	
30 35	1 Gly	Ser Trp	Ser Lys	Ile Lys 20	Leu 5 Ser	Pro Ala	Phe Gly	Thr Gly	Pro Ser 25	Pro 10 Gly	Val Gly	Val Ala	Gly	Gly 30	15 Gly	Glu	
	l Gly Gln	Ser Trp Asn	Ser Lys Gly 35	Ile Lys 20 Gln	Leu 5 Ser Glu	Pro Ala Glu	Phe Gly Lys	Thr Gly Trp 40	Pro Ser 25 Cys	Pro 10 Gly	Val Gly Lys	Val Ala Ala	Gly Val 45	Gly 30 Lys	15 Gly Ser	Glu Leu	
35	1 Gly Gln Val	Ser Trp Asn Lys 50	Ser Lys Gly 35 Lys	Ile Lys 20 Gln Leu	Leu 5 Ser Glu Lys	Pro Ala Glu Lys	Phe Gly Lys Thr 55	Thr Gly Trp 40 Gly	Pro Ser 25 Cys Arg	Pro 10 Gly Glu Leu	Val Gly Lys Asp	Val Ala Ala Glu 60	Gly Val 45 Leu	Gly 30 Lys Glu	15 Gly Ser Lys	Glu Leu Ala	
	1 Gly Gln Val Ile 65	Ser Trp Asn Lys 50 Thr	Ser Lys Gly 35 Lys Thr	Ile Lys 20 Gln Leu Gln	Leu 5 Ser Glu Lys Asn	Pro Ala Glu Lys Cys 70	Phe Gly Lys Thr 55 Asn	Thr Gly Trp 40 Gly Thr	Pro Ser 25 Cys Arg	Pro 10 Gly Glu Leu Cys	Val Gly Lys Asp Val	Val Ala Ala Glu 60 Thr	Gly Val 45 Leu Ile	Gly 30 Lys Glu Pro	15 Gly Ser Lys Ser	Glu Leu Ala Thr	
35	1 Gly Gln Val Ile 65 Cys	Ser Trp Asn Lys 50 Thr	Ser Lys Gly 35 Lys Thr	Ile Lys 20 Gln Leu Gln Ile	Leu 5 Ser Glu Lys Asn Trp	Pro Ala Glu Lys Cys 70 Gly	Phe Gly Lys Thr 55 Asn	Thr Gly Trp 40 Gly Thr	Pro Ser 25 Cys Arg Lys	Pro 10 Gly Glu Leu Cys Pro 90	Val Gly Lys Asp Val 75 Asn	Val Ala Ala Glu 60 Thr	Gly Val 45 Leu Ile	Gly 30 Lys Glu Pro	15 Gly Ser Lys Ser Gln 95	Glu Leu Ala Thr 80 Trp	
35	1 Gly Gln Val Ile 65 Cys	Ser Trp Asn Lys 50 Thr Ser	Ser Lys Gly 35 Lys Thr Glu Thr	Lys 20 Gln Leu Gln Ile Gly 100	Leu 5 Ser Glu Lys Asn Trp 85 Leu	Pro Ala Glu Lys Cys 70 Gly Tyr	Phe Gly Lys Thr 55 Asn Leu Ser	Thr Gly Trp 40 Gly Thr Ser	Pro Ser 25 Cys Arg Lys Thr Ser 105	Pro 10 Gly Glu Leu Cys Pro 90 Glu	Val Gly Lys Asp Val 75 Asn	Val Ala Ala Glu 60 Thr Thr	Gly Val 45 Leu Ile Ile Arg	Gly 30 Lys Glu Pro Asp Ser 110	15 Gly Ser Lys Ser Gln 95 Leu	Glu Leu Ala Thr 80 Trp Asp	
35 40	1 Gly Gln Val Ile 65 Cys Asp	Ser Trp Asn Lys 50 Thr Ser Thr	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val	Pro Ala Glu Lys Cys 70 Gly Tyr Ser	Phe Gly Lys Thr 55 Asn Leu Ser	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys	Pro 10 Gly Glu Leu Cys Pro 90 Glu	Val Gly Lys Asp Val 75 Asn Gln Leu	Val Ala Ala Glu 60 Thr Thr Pro	Gly Val 45 Leu Ile Ile Arg His 125	Gly 30 Lys Glu Pro Asp Ser 110 Val	15 Gly Ser Lys Ser Gln 95 Leu	Glu Leu Ala Thr 80 Trp Asp	
35 40 45	1 Gly Gln Val Ile 65 Cys Asp Gly Cys	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp	Phe Gly Lys Thr 55 Asn Leu Ser His Pro	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys Leu	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly	Val Gly Lys Asp Val 75 Asn Gln Leu Ser	Val Ala Ala Glu 60 Thr Thr Thr Ala Ala	Gly Val 45 Leu Ile Ile Arg His 125 His	Gly 30 Lys Glu Pro Asp Ser 110 Val	15 Gly Ser Lys Ser Gln 95 Leu Ile	Glu Leu Ala Thr 80 Trp Asp Tyr Lys	
35 40	1 Gly Gln Val Ile 65 Cys Asp Gly Cys Ala 145	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg 130 Ile	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu Glu	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp Asn	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp Glu 150	Phe Gly Lys Thr 55 Asn Leu Ser His Pro 135	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys Leu Phe	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly His	Val Gly Lys Asp Val 75 Asn Gln Leu Ser Leu 155	Val Ala Ala Glu 60 Thr Thr Thr 140 Lys	Gly Val 45 Leu Ile Ile Arg His 125 His	Gly 30 Lys Glu Pro Asp Ser 110 Val Glu Asp	15 Gly Ser Lys Ser Gln 95 Leu Ile Leu	Glu Leu Ala Thr 80 Trp Asp Tyr Lys Val 160	
35 40 45	1 Gly Gln Val Ile 65 Cys Asp Gly Cys Ala 145	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg 130 Ile	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu Glu	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp Glu 150	Phe Gly Lys Thr 55 Asn Leu Ser His Pro 135	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys Leu Phe	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly His	Val Gly Lys Asp Val 75 Asn Gln Leu Ser Leu 155	Val Ala Ala Glu 60 Thr Thr Thr 140 Lys	Gly Val 45 Leu Ile Ile Arg His 125 His	Gly 30 Lys Glu Pro Asp Ser 110 Val Glu Asp	15 Gly Ser Lys Ser Gln 95 Leu Ile Leu	Glu Leu Ala Thr 80 Trp Asp Tyr Lys Val 160 Pro	
35 40 45	1 Gly Gln Val Ile 65 Cys Asp Gly Cys Ala 145 Cys	Ser Trp Asn Lys 50 Thr Ser Thr Arg Arg 130 Ile Val	Ser Lys Gly 35 Lys Thr Glu Thr Leu 115 Leu Glu Asn	Ile Lys 20 Gln Leu Gln Ile Gly 100 Gln Trp Asn	Leu 5 Ser Glu Lys Asn Trp 85 Leu Val Arg Cys Tyr 165	Pro Ala Glu Lys Cys 70 Gly Tyr Ser Trp Glu 150 His	Phe Gly Lys Thr 55 Asn Leu Ser His Pro 135 Tyr	Thr Gly Trp 40 Gly Thr Ser Phe Arg 120 Asp Ala Gln	Pro Ser 25 Cys Arg Lys Thr Ser 105 Lys Leu Phe Arg	Pro 10 Gly Glu Leu Cys Pro 90 Glu Gly His Asn Val	Val Gly Lys Asp Val 75 Asn Gln Leu Ser Leu 155 Glu	Val Ala Ala Glu 60 Thr Thr Thr 140 Lys Thr	Gly Val 45 Leu Ile Ile Arg His 125 His Lys Pro	Gly 30 Lys Glu Pro Asp Ser 110 Val Glu Asp Val	Ser Lys Ser Gln 95 Leu Ile Leu Glu Leu 175	Glu Leu Ala Thr 80 Trp Asp Tyr Lys Val 160 Pro	

			195					200					205			
	Gly	Ile 210		Pro	Gln	Ser	Asn 215		Ile	Pro	Glu	Thr 220		Pro	Pro	Gly
5	Tyr 225		Ser	Glu	Asp	Gly 230		Thr	Ser	Asp	Gln 235		Leu	Asn	Gln	Ser 240
		Asp	Thr	Gly	Ser 245	Pro	Ala	Glu	Leu	Ser 250	Pro	Thr	Thr	Leu	Ser 255	Pro
	Val	Asn	His	Ser 260	Leu	Asp	Leu	Gln	Pro 265	Val	Thr	Tyr	Ser	Glu 270	Pro	Ala
10	Phe	Trp	Cys 275	Ser	Ile	Ala	Tyr	Tyr 280	Glu	Leu	Asn	Gln	Arg 285	Val	Gly	Glu
	Thr	Phe 290	His	Ala	Ser	Gln	Pro 295	Ser	Leu	Thr	Val	Asp 300	Gly	Phe	Thr	Asp
15	Pro 305	Ser	Asn	Ser	Glu	Arg 310	Phe	Cys	Leu	Gly	Leu 315	Leu	Ser	Asn	Val	Asn 320
	Arg	Asn	Ala	Thr	Val 325	Glu	Met	Thr	Arg	Arg 330	His	Ile	Gly	Arg	Gly 335	Val
	Arg	Leu	Tyr	Tyr 340	Ile	Gly	Gly	Glu	Val 345	Phe	Ala	Glu	Cys	Leu 350	Ser	Asp
20	Ser	Ala	Ile 355	Phe	Val	Gln	Ser	Pro 360	Asn	Cys	Asn	Gln	Arg 365	Tyr	Gly	Trp
		370				_	375				•	380		Leu		
25	Phe 385	Asn	Asn	Gln	Glu	Phe 390	Ala	Ala	Leu	Leu	Ala 395	Gln	Ser	Val	Asn	Gln 400
	Gly	Phe	Glu	Ala	Val 405	Tyr	Gln	Leu	Thr	Arg 410	Met	Cys	Thr	Ile	Arg 415	Met
				420	_	_	_		425	_	_	_		Thr 430		
30			435	_				440					445	Leu		
	Leu	Asp 450	Lys	Val	Leu	Thr	Gln 455	Met	Gly	Ser	Pro	Ser 460	Val	Arg	Cys	Ser
35	465			-		470				_	475			Ala		480
	Val	Ser	Lys	Gly	Glu 485	Glu	Leu	Phe	Thr	Gly 490	Val	Val	Pro	Ile	Leu 495	Val
	Glu	Leu	Asp	Gly 500	Asp	Val	Asn	Gly	His 505	Lys	Phe	Ser	Val	Ser 510	Gly	Glu
40	_		515					520					525			Cys
		530	_	_			535					540				Leu
45	545	_	_			550			_		555					Gln 560
		_			565					570	· .			Gln	575	
				580					585					590		Val
50			595	=				600					605	Lys		
	_	610	-				615			_		620				Asn
55	625					630					635					Gly 640
	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val

	Gln	Leu	Ala	_	645 His	Tyr	Gln	Gln		650 Thr	Pro	Ile	Gly		655 Gly	Pro	
-	Val	Leu	Leu	660 Pro	Asp	Asn	His	_	665 Leu	Ser	Thr	Gln		670 Ala	Leu	Ser	
5	Lys	Asp 690	675 Pro	Asn	Glu	Lys	Arg 695	680 Asp	His	Met	Val	Leu 700	685 Leu	Glu	Phe	Val	
10	Thr 705		Ala	Gly	Ile	Thr 710		Gly	Met	Asp	Glu 715		Tyr	Lys			
.0			(2)	INE	ORMA	MOITA	1 FOF	SEC) ID	NO:7	76:						
15		(i	(B) (C)	EQUEN LENC TYPE STRA TOPO	STH: E: nu ANDEI	2397 iclei NESS	bas c ac s: si	se pa cid ingle	airs								
20		-	li) M lx) F			TYPE	E: cI	ANC									
25		(2	(B)	NAM LOC OTH	CATIC HER I	N: 1	RMATI	2394 ION:			NO : 7	76:					
30		GAC	AAT Asn	ATG	TCT	ATT	ACG	TAA	ACA	CCA	ACA	AGT					48
35			ATT Ile														96
			TTT Phe 35														144
40			AAA Lys														192
45			CAT His														240
50			CAG Gln														288
5.E			TGG Trp														336
55	AAA	TAT	TGT	CAG	TAT	GCG	TTT	GAC	TTA	AAA	TGT	GAT	AGT	GTC	TGT	GTG	384

	Lys	Tyr	Cys 115	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Cys	Asp	Ser 125	Val	Cys	Val		
5					TAC Tyr												432,	
10					CAG Gln												480	
4.5					GAC Asp 165												528	
15					ACC Thr												576	
20					ACC Thr												624	
25					AAC Asn												672	
30					CTG Leu												720	
					CAG Gln 245												768	
35					CAT His												816	
40					ACA Thr												864	
45					CCT Pro												912	
50					GCA Ala												960	
					TCC Ser 325												1008	
55	GAG	ACA	TTT	AAG	GTT	CCT	TCA	AGC	TGC	CCT	ATT	GTT	ACT	GTT	GAT	GGA	1056	173

										1/4							
	Glu	Thr	Phe	Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly	
5												TTG Leu					1104
10	_											AGG Arg 380				_	1152
15												GAT Asp					1200
13												TAC Tyr					1248
20												AAG Lys					1296
25												CAT His				_	1344
30												GCC Ala 460					1392
35												GGT Gly					1440
33												GTT Val					1488
40												GGC Gly		_			1536
45												TGG Trp					1584
50												CTT Leu 540					1632
55												CCG Pro					1680
	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	GTC	1728

										1/5								
	Val	Ser	Lys	Gly	Glu 565	Glu	Leu	Phe	Thr	Gly 570	Val	Val	Pro	Ile	Leu 575	Val		
5		CTG Leu															1776	
				580					585					590				
10		GAG Glu															1824	
10	ACC	ACC		AAG	CTG	CCC	GTG		TGG	CCC	ACC	CTC		ACC	ACC	CTG	1872	
4.5	Thr	Thr 610	Gly	Lys	Leu	Pro	Val 615	Pro	Trp	Pro	Thr	Leu 620	Val	Thr	Thr	Leu		
15		TAC Tyr															1920	
	625	-3-	1			630			J	-1-	635				-1-	640		
20		GAC Asp															1968	• !
	ACC	ATC	TTC	TTC		GAC	GAC	GGC	AAC		AAG	ACC	CGC	GCC		GTG	20~16	
25	Thr	Ile	Phe	Phe 660	Lys	Asp	Asp	Gly	Asn 665	Tyr	Lys	Thr	Arg	Ala 670	Glu	Val		
		TTC Phe															2064	
30	-7-		675	1	E			680		5			685	-1-	1			
		TTC Phe 690															2112	
35	ፕልር	AAC	AGC	CAC	AAC	GTC		АТС	ΔTG	GCC	GAC		CAG	AAG	AAC	GGC	2160	
		Asn															2200	
40		AAG Lys															2208	
		_,,			725	2,0			*****	730	110	-		1	735			
45		CTC Leu		Asp					Asn					Asp			2256	·
	GTG	CTG	CTG	740 CCC	GAC	AAC	CAC	TAC	745 CTG	AGC	ACC	CAG	TCC	750 GCC	CTG	AGC	2304	
50		Leu																
		GAC Asp															2352	
55	-,-	770	_ ~ •		-	·	775	P		- , 		780						• .
	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AAG	TAA		2397	175

176

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 785 790 795

- 5 (2) INFORMATION FOR SEQ ID NO:77:
 - (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 798 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal

15

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

	Met 1	Asp	Asn	Met	Ser 5	Ile	Thr	Asn	Thr	Pro 10	Thr	Ser	Asn	Asp	Ala 15	Cys
20			Ile	20					25		_		-	30		
			Phe 35					40					45			
25		50	Lys				55					60				
	Gly 65	Ala	His	Pro	Ser	Lys 70	Cys	Val	Thr	Ile	Gln 75	Arg	Thr	Leu	Asp	Gly 80
	Arg	Leu	Gln	Val	Ala 85	Gly	Arg	Lys	Gly	Phe 90	Pro	His	Val	Ile	Tyr 95	Ala
30	Arg	Leu	Trp	Arg 100	Trp	Pro	Asp	Leu	His 105	Lys	Asn	Glu	Leu	Lys 110	His	Val
		_	Cys 115		_			120		_	-	-	125		_	
35		130	Tyr				135					140		_		
	Gly 145	Leu	Thr	Leu	Gln	Ser 150	Asn	Ala	Pro	Ser	Ser 155	Met	Met	Val	Lys	Asp 160
	Glu	Tyr	Val	His	Asp 165	Phe	Glu	Gly	Gln	Pro 170	Ser	Leu	Ser	Thr	Glu 175	Gly
40	His	Ser	Ile	Gln 180	Thr	Ile	Gln	His	Pro 185	Pro	Ser	Asn	Arg	Ala 190	Ser	Thr
	Glu	Thr	Tyr 195	Ser	Thr	Pro	Ala	Leu 200	Leu	Ala	Pro	Ser	Glu 205	Ser	Asn	Ala
45	Thr	Ser 210	Thr	Ala	Asn	Phe	Pro 215	Asn	Ile	Pro	Val	Ala 220	Ser	Thr	Ser	Gln
	Pro 225	Ala	Ser	Ile	Leu	Gly 230	Gly	Ser	His	Ser	Glu 235	Gly	Leu	Leu	Gln	Ile 240
	Ala	Ser	Gly	Pro	Gln 245	Pro	Gly	Gln	Gln	Gln 250		Gly	Phe	Thr	Gly 255	Gln
50	Pro	Ala	Thr	Tyr 260	His	His	Asn	Ser	Thr 265	Thr	Thr	Trp	Thr	Gly 270	Ser	Arg
	Thr	Ala	Pro 275	Tyr	Thr	Pro	Asn	Leu 280	Pro	His	His	Gln	Asn 285	Gly	His	Leu
55	Gln	His 290	His	Pro	Pro	Met	Pro 295	Pro	His	Pro	Gly	His 300	Tyr	Trp	Pro	Val
	His	Asn	Glu	Leu	Ala	Phe	Gln	Pro	Pro	Ile	Ser	Asn	His	Pro	Ala	Pro

										,,,						
	305					310					315					320
	Glu	Tyr	Trp	Cys	Ser 325	Ile	Ala	Tyr	Phe	Glu 330	Met	Asp	Val	Gln	Val 335	Gly
5	Glu	Thr	Phe	Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly
	Tyr	Val	Asp 355	Pro	Ser	Gly	Gly	Asp 360	Arg	Phe	Cys	Leu	Gly 365	Gln	Leu	Ser
	Asn	Val 370	His	Arg	Thr	Glu	Ala 375	Ile	Glu	Arg	Ala	Arg 380	Leu	His	Ile	Gly
10	Lys 385	Gly	Val	Gln	Leu	Glu 390	Cys	Lys	Gly	Glu	Gly 3 95	Asp	Val	Trp	Val	Arg 400
	Cys	Leu	Ser	Asp	His 405	Ala	Val	Phe	Val	Gln 410	Ser	Tyr	Tyr	Leu	Asp 415	Arg
15	Glu	Ala	Gly	Arg 420	Ala	Pro	Gly	Asp	Ala 425	Val	His	Lys	Ile	Tyr 430	Pro	Ser
		_	435					440					445	Gln		
		450					455					460		Ala		
20	465					470					475			Ile		480
					485				-	490	_		_	Asp	495	_
25			_	500					505					Gly 510		
	_		515				_	520					525	Glu		
		530	_				535		_			540		Thr		
30	545					550					555			Ala		560
				_	565					570				Ile	575	
35				580					585					Ser 590		
			595					600					605	Phe		Leu
40		610					615					620				Gln
40	625					630					635					640 Arg
		_			645					650	_				655	Val
45	•			660					665					670		Ile
	_		675					680					685			Asn
50		690					695					700				Gly
	705					710					715			Gly	,	720
					725					730					735	Pro
55				740					745					750 Ala		

										178								
			755					760					765					
	Lys	Asp 770	Pro	Asn	Glu	Lys	Arg 775	Asp	His	Met	Val	Leu 780	Leu	Glu	Phe	Val		
5	Thr 785	Ala	Ala	Gly	Ile	Thr 790	Leu	Gly	Met	Asp	Glu 795	Leu	Tyr	Lys				
			(2)	INF	ORMA	MOITA	FOR	SEC) ID	NO:7	8:							
10		(i	(A) (B) (C)	EQUEN LENC TYPE STRA TOPO	TH: : nu .NDEL	3138 iclei NESS	bas c ac : si	e pa id ngle	irs									
15		-		OLEC		TYPE	E: cD	NA										
20			(B)	NAN LOC OTI	CATIC)N: 1	3	135	equen	ice								
		()	(i) S	EQUE	ENCE	DESC	CRIPT	: NOI	SEC) ID	NO: 7	78:						
25		GCG Ala															48	
30		ATG Met															96	
		TTG. Leu															144	
35		AAT Asn 50															192	
40		CAG Gln															240	
45		TTA Leu													_		288	
50		TAT Tyr															336	
55		TAC Tyr															384	
3 5	CCG	GCT	GGG	ATC	CTG	GTT	GAC	GCC	ATG	TCC	CAG	AAG	CAC	CTT	CAG	ATC	432	178

	Pro	Ala 130	Gly	Ile	Leu	Val	Asp 135	Ala	Met	Ser	Gln	Lys 140	His	Leu	Gln	Ile	
5		CAG Gln															480
10		CTG Leu															528
	_	GAG Glu															576
15		CCC Pro														_	624
20		TCT Ser 210															672
25		CGC Arg															720
30		AAG Lys															768
35		CGG Arg															816
		GTG Val															864
40		CGG Arg 290															912
45		CCC Pro															960
50		GAC Asp															1008
55		CCT Pro															1056
55	CGC	CTG	CTG	GTG	GGC	GGG	AAG	CTG	AAC	GTG	CAC	ATG	AAT	CCC	CCC	CAG	1104

	Ara	Leu	Leu	Val	Glv	Glv	Lvs	Leu	Asn	Val	His	Met	Asn	Pro	Pro	Gln	
	5		355		1	1	-,-	360					365			-	
5		AAG															1152
5	Val	Lys 370	Ala	Int	116	ше	375	GIU	GIN	GIN	АТА	380	ser	ьeu	Leu	гÀг	
		GAG															1200
10	385	Glu	ASII	1111	Arg	390	GIU	Cys	ser	GIY	395	116	ьеи	ASII	ASII	400	
		GTG Val															1248
15	•				405					410					415		
13	AGG	AAC	ATG	TCA	CTG	AAG	AGG	ATC	AAG	CGT	GCT	GAC	CGG	CGG	GGT	GCA	1296
	Arg	Asn	Met	Ser 420	Leu	Lys	Arg	Ile	Lys 425	Arg	Ala	Asp	Arg	Arg 430	Gly	Ala	
20		TCC															1344
	GIU	Ser	435	inr	GIU	GIU	гÀг	440	Thr	vai	ьeu	Pne	445	ser	GIN	Pne	
25		GTT Val															1392
		450	1				455	•41	1	0111	vui	460	****	200	001	200	
		GTG Val															1440
30 .	465					470		2			475					480	
		GTG Val															1488
	1111	vai	Бец	пр	485	ASII	Ala	FIIC	Ald	490	PIO	GIY	ALG	vai	495	FIIC	
35	GCC	GTG	CCT	GAC	AAA	GTG	CTG	TGG	CCG	CAG	CTG	TGT	GAG	GCG	CTC	AAC	1536
	Ala	Val	Pro	Asp 500	Lys	Val	Leu	Trp	Pro 505	Gln	Leu	Cys	Glu	Ala 510	Leu	Ąsn	
40		AAA															1584
	Met	Lys	Pne 515	гàг	Ala	Glu	Val	G1n 520	Ser	Asn	Arg	Gly	Leu 525	Thr	Lys	GIu	
45		CTC															1632
45	ASI	Leu 530	vai	Pne	ьeu	Ala	535	ьуs	Leu	Phe	Asn	Asn 540	ser	ser	ser	HIS	
		GAG Glu					-						-	-			1680
50	545		· F	-1-		550					555		~-··			560	
		AAC															1728
	Glu	Asn	Leu	Pro	Gly 565	Trp	Asn	Tyr	Thr	Phe 570	Trp	Gln	Trp	Phe	Asp 575	Gly	
55	GTG	ATG	GAG	GTG	ጥጥር፤	AVG	ΔΔα	כאכ	CAC		רככ	CAC	тсс	ልአጥ	ርአጥ	GGG	1776
	- 1 -	0	Crau	010	110		770	CAC	CAC	AAG		CAC	130	WYI	JAI	300	1,70

										101							
	Val	Met	Glu	Val 580	Leu	Lys	Lys	His	His 585	Lys	Pro	His	Trp	Asn 590	Asp	Gly	
	GCC	ATC	СТА	GGT	TTT	GTG	ААТ	AAG	CAA	CAG	GCC	CAC	GAC	CTG	CTC	ATC	1824
5					Phe									_			
	AAC	AAG	כככ	GAC	GGG	ACC	ттс	ттс	ттс	רפר	ידידידי	AGT	GAC	тса	GAA	ATC	1872
					Gly												20.2
10		610		_			615					620					
					ATC												1920
	625	GIA	lie	Thr	Ile	630	Trp	гàг	Pne	Asp	635	Pro	GIU	Arg	Asn	ьеи 640	
15	023					030					033					040	
, 0	TGG	AAC	CTG	AAA	CCA	TTC	ACC	ACG	CGG	GAT	TTC	TCC	ATC	AGG	TCC	CTG	1968
	Trp	Asn	Leu	Lys	Pro	Phe	Thr	Thr	Arg	Asp	Phe	Ser	Ile	Arg	Ser	Leu	
					645					650					655		
20	CCT	GAC	CGG	СТС	GGG	GAC	CTG	AGC	тат	СТС	ΔΤС	тдт	GTG	יגיניני	CCT	GAC	2016
20					Gly												2010
		•	J	660	-	•			665			-		670	٠	-	
25					GAG												2064
25	arg	Pro	ьуs 675	Asp	Glu	vai	Pne	5er 680	ьуѕ	Tyr	Tyr	Thr	685	vai	Leu	Ala	•
			0,5					000					005				
	AAA	GCT	GTT	GAT	GGA	TAT	GTG	AAA	CCA	CAG	ATC	AAG	CAA	GTG	GTC	CCT	2112
00	Lys		Val	Asp	Gly	Tyr		Lys	Pro	Gln	Ile	_	Gln	Val	Val	Pro	
30		690					695					700					
	GAG	TTT	GTG	AAT	GCA	TCT	GCA	GAT	GCT	GGG	GGC	AGC	AGC	GCC	ACG	TAC	2160
	Glu	Phe	Val	Asn	Ala	Ser	Ala	Asp	Ala	Gly	Gly	Ser	Ser	Ala	Thr	Tyr	
	705					710					715					720	
35	3 m/c	a n a	~ ~ ~	GGG	CCC	maa	CCA	CCT	CTC.	таа	CCC	CAC	COTT	ccc	יייאייי	7 7 C	2208
					Pro												2208
		пор	0111	1114	725	001		•••-		730					735		
40					AAC												2256
	мес	Tyr	Pro	740	Asn	Pro	Asp	HIS	745	Leu	Asp	GIN	Asp	750	GIU	Pne	
				, 10					, 13					, 50			
	GAC	CTG	GAT	GAG	ACC	ATG	GAT	GTG	GCC	AGG	CAC	GTG	GAG	GAA	CTC	TTA	2304
45	Asp	Leu	-	Glu	Thr	Met	Asp		Ala	Arg	His	Val		Glu	Leu	Leu	
			755					760					765				
	CGC	CGA	CCA	ATG	GAC	AGT	CTT	GAC	TCC	CGC	CTC	TCG	CCC	CCT	GCC	GGT	2352
					Asp												
50	_	770			-		775	-		_		780					
			N ~~	m-c=	~~~	707	000	ma~	~~~	ma-	ma-	Omr		C CC	000	CCC	2400
					GCC Ala												2400
	785	FIIG	TILL	JEL	AIG	790	Сту	261	neu	JEL	795	val	110	n. 9	AIU	800	
55																	
	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	2448
																	11

182

										182							
	Asp	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr	
5		GTG Val															2496
10		TTC Phe															2544
15		ACC Thr 850															2592
		ACC Thr															2640
20		CCC Pro															2688
2 5		GGC Gly															2736
30		AAG Lys															2784
35		ATC Ile 930															2832
		CAC His															2880
40		GAC Asp															2928
45		ATC Ile															2976
50		CCC Pro					Pro					Asp					3024
55	Ser	ACC Thr 1010				Leu					Asn					_	3072
- +	ATG	GTC	CTG	CTG	GAG	TTC	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	3120

182

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										183							
	Met 1025	Val	Leu	Leu	Glu	Phe 1030	Val	Thr	Ala		Gly 1035	Ile	Thr	Leu		Met 1040	
5				Tyr	AAG Lys 1045	TAA											3138
10			(2)) INI	FORM	OITA	N FOI	R SE	Q ID	NO:	79:						
10		(:	(A) (B)	LENG TYPI	NCE (GTH: E: ar	1049 mino	acio	ino a	acids	5							
15			(D)	TOP	OLOG	Y: 1:	inea	r									
					CULE ENT		-										
20		(:	xi) {	SEQUI	ENCE	DESC	CRIP:	rion	: SE	Q ID	NO:	79:				•	
	1		-	_	Ile 5					10		_	_		15	_	
25	Gln	Met	Gln	Val 20	Leu	Tyr	Gly	Gln	His 25	Phe	Pro	Ile	Glu	Val 30	Arg	His	*: '
	Tyr	Leu	Ala 35	Gln	Trp	Ile	Glu	Ser 40	Gln	Pro	Trp	Asp	Ala 45	Ile	Asp	Leu	
	Asp	Asn 50	Pro	Gln	Asp	Arg	Ala 55	Gln	Ala	Thr	Gln	Leu [.] 60	Leu	Glu	Gly	Leu	
30	Val 65	Gln	Glu	Leu	Gln	Lys 70	Lys	Ala	Glu	His	Gln 75	Val	Gly	Glu	Asp	Gly 80	
		Leu	Leu	Lys	Ile 85		Leu	Gly	His	Tyr 90		Thr	Gln	Leu	Gln 95		
35	Thr	Tyr	Asp	Arg 100	Cys	Pro	Leu	Glu	Leu 105		Arg	Cys	Ile	Arg 110		Ile	
	Leu	Tyr	Asn 115		Gln	Arg	Leu	Val 120		Glu	Ala	Asn	Asn 125		Ser	Ser	
	Pro	Ala 130		Ile	Leu	Val	Asp		Met	Ser	Gln	Lys 140		Leu	Gln	Ile	
40	Asn 145		Thr	Phe	Glu	Glu 150		Arg	Leu	Val	Thr 155		Asp	Thr	Glu	Asn 160	
		Leu	Lys	Lys	Leu 165		Gln	Thr	Gln	Glu 170		Phe	Ile	Ile	Gln 175		
45	Gln	Glu	Ser	Leu 180	Arg	Ile	Gln	Ala	Gln 185		Ala	Gln	Leu	Ala 190		Leu	
40	Ser	Pro	Gln 195		Arg	Leu	Ser	Arg 200		Thr	Ala	Leu	Gln 205		Lys	Gln	
	Val	Ser 210		Glu	Ala	Trp	Leu 215		Arg	Glu	Ala	Gln 220		Leu	Gln	Gln	
50	_		Val	Glu	Leu			Lys	His	Gln	_		Leu	Gln	Leu		
	225 Arg	Lys	Gln	Gln	Thr	230 Ile	Ile	Leu	Asp	Asp	235 Glu	Leu	Ile	Gln	Trp	240 Lys	
					245 Leu				_	250					255		
55				260					265	_				270			. •
	Asp	val	Leu	GIn	Ser	Trp	Cys	Glu	ьуs	Leu	Ala	Glu	тте	TIE	Trp	GIN	

			275					280					285			
	Asn	Ara		Gln	Ile	Ara	Ara		Glu	His	Len	Cvs		Gln	Len	Pro
		290				5	295		014			300	01	01		110
	Ile	Pro	Gly	Pro	Val	Glu	Glu	Met	Leu	Ala	Glu	Val	Asn	Ala	Thr	Ile
5	305					310					315					320
	Thr	Asp	Ile	Ile	Ser	Ala	Leu	Val	Thr	Ser	Thr	Phe	Ile	Ile	Glu	Lys
		_	_		325	_		_	_	330				_	335	
	GIn	Pro	Pro		Val	Leu	Lys	Thr	Gln	Thr	Lys	Phe	Ala		Thr	Val
10	λνα	Len	T.e.u	340	Cly	Cly	Lvc	Lou	345 Asn	v. l	ui a	Mo+	7 ~ ~	350	Dwo	C12
	Arg	bcu	355	Vai	Gry	GLY	цуз	360	ASII	vai	птэ	MEC	365	PIO	PIO	GIII
	Val	Lys		Thr	Ile	Ile	Ser		Gln	Gln	Ala	Lys		Leu	Leu	Lys
		370					375					380				•
	Asn	Glu	Asn	Thr	Arg	Asn	Glu	Cys	Ser	Gly	Glu	Ile	Leu	Asn	Asn	Cys
15	385					390					395					400
	Cys	Val	Met	Glu		His	Gln	Ala	Thr		Thr	Leu	Ser	Ala		Phe
	7	N	14 a b	C	405	T	7	T1 -	•	410					415	7.7 -
	Arg	ASII	Mec	420	Leu	ьys	Arg	ile	Lys 425	Arg	Ата	Asp	Arg	Arg 430	GIA	Ala
20	Glu	Ser	Val		Glu	Glu	Lvs	Phe	Thr	Val	Leu	Phe	Glu		Gln	Phe
			435				-,-	440					445	-		
	Ser	Val	Gly	Ser	Asn	Glu	Leu	Val	Phe	Gln	Val	Lys	Thr	Leu	Ser	Leu
		450					455					460				
		Val	Val	Val	Ile		His	Gly	Ser	Gln	_	His	Asn	Ala	Thr	Ala
25	465	17- 3	¥			470		-1			475	~ 3	_		_	480
	Thr	vai	Leu	Trp	485	Asn	АТА	Pne	Ala	G1u 490	Pro	GIY	Arg	Val	Pro 495	Pne
	Ala	Val	Pro	Asp		Val	Leu	Tro	Pro		Leu	Cvs	Glu	Δla		Asn
				500	-1-				505			0,0		510		
30	Met	Lys	Phe	Lys	Ala	Glu	Val	Gln	Ser	Asn	Arg	Gly	Leu	Thr	Lys	Glu
			515					520					525			
	Asn		Val	Phe	Leu	Ala		Lys	Leu	Phe	Asn		Ser	Ser	Ser	His
	T 011	530	7.00	771.50	Com	<i>α</i> 1	535	~	17- 1	0		540	Q1	Dh.a	N	7
35	545	Giu	Asp	TAT	ser	550	Leu	ser	Val	ser	555	ser	GIN	Pne	ASI	560
		Asn	Leu	Pro	Gly		Asn	Tyr	Thr	Phe		Gln	Trp	Phe	Asp	
					565	-		•		570	-		-		575	•
	Val	Met	Glu	Val	Leu	Lys	Lys	His	His	Lys	Pro	His	Trp	Asn	Asp	Gly
40				580		_			585					590		
40	Ala	Ile		Gly	Phe	Val	Asn	-	Gln	Gln	Ala	His	-	Leu	Leu	Ile
	Λen	Laze	595 Pro	Λen	Glv	Thr	Dhe	600	Leu	7 ~~	Dho	202	605	Co.~	C1.,	τ10
	MSII	610	PIO	ASD	Gry	1111	615	Leu	Leu	Arg	Pne	620	Asp	sei	GIU	iie
	Gly		Ile	Thr	Ile	Ala		Lvs	Phe	Asp	Ser		Glu	Ara	Asn	Leu
45	625	-				630	~	•		_	635					640
	Trp	Asn	Leu	Lys	Pro	Phe	Thr	Thr	Arg	Asp	Phe	Ser	Ile	Arg	Ser	Leu
					645					650					655	
	Ala	Asp	Arg		Gly	Asp	Leu	Ser	Tyr	Leu	Ile	Tyr	Val		Pro	Asp
50	λ ~~ ~	Dro	T	660	C1	17-1	Dh.	0	665			m\	D	670	T	71-
30	Arg	PIO	675	Asp	Giu	vai	Pne	5er 680	Lys	Tyr	Tyr	rnr	685	vai	Leu	Ala
	Lys	Ala		Asp	Gly	Tyr	Val		Pro	Gln	Ile	Lvs		Val	Val	Pro
	4	690			- 3		695	-1-				700				
		Phe	Val	Asn	Ala	Ser	Ala	Asp	Ala	Gly	Gly	Ser	Ser	Ala	Thr	Tyr
55	705	_			_	710					715	_				720
	Met	Asp	Gln	Ala	Pro	Ser	Pro	Ala	Val	Cys	Pro	Gln	Ala	Pro	Tyr	Asn

					725					730					735				
	Met	Tyr	Pro	Gln 740	Asn	Pro	Asp	His	Val 745	Leu	Asp	Gln	Asp	Gly 750	Glu	Phe			
5	Asp	Leu	Asp 755	Glu	Thr	Met	Asp	Val 760	Ala	Arg	His	Val	Glu 765	Glu	Leu	Leu		•	
	Arg	Arg 770	Pro	Met	Asp	Ser	Leu 775	Asp	Ser	Arg	Leu	Ser 780	Pro	Pro	Ala	Gly			
	Leu 785	Phe	Thr	Ser	Ala	Arg 790	Gly	Ser	Leu	Ser	Trp 795	Val	Pro	Arg	Ala	Arg 800			
10	Asp	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr			
	Gly	Val	Val	Pro 820	Ile	Leu	Val	Glu	Leu 825	Asp	Gly	Asp	Val	Asn 830	Gly	His			
15	Lys	Phe	Ser 835	Val	Ser	Gly	Glu	Gly 840	Glu	Gly	Asp	Ala	Thr 845	Tyr	Gly	Lys			
	Leu	Thr 850	Leu	Lys	Phe	Ile	Cys 855	Thr	Thr	Gly	Lys	Leu 860	Pro	Val	Pro	Trp			
	865	Thr				870			_	_	875		_			880			
20	Tyr	Pro	Asp	His	Met 885	Lys	Gln	His	Asp	Phe 890	Phe	Lys	Ser	Ala	Met 895	Pro			
		Gly		900			_		905			-	_	910	-				
25		Lys	915					920					925					• •	
		Ile 930					935	_		_		940	_					1	
	945	His				950					955			_		960		*	
30		Asp			965		_		_	970		•	-		975			÷	
		Ile		980					985		_		_	990					
35		Pro	995				:	1000				:	1005					₹.,	
	:	1010					L015				-	1020	-			His	•		
40	025	Val			:	1030	vai	Thr	АТА		G1y 1035	iie	Thr	Leu		Mec 1040			
40	Asp	Glu	neu		1045														
			(2)	INI	FORM	OITA	1 FOI	R SE	O ID	NO:8	30:								
45		(j		EQUEI LENC															
			(B)	TYPE	E: ni	ıcle	ic ad	cid											
50				TOP				_											
		()	ci) S	SEQUI	ENCE	DESC	CRIPT	rion	: SE(O ID	NO:8	30:						•	
	TGG	GATC							.,									28	
55			(2)) INI	FORM	OITA	1 FOI	R SE(Q ID	NO : 8	31:								•
																			185

5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
	(b) Toronogr. Timedi	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81: GTCTCGAGGG AGCATGGGCA CCTTGCG	27
	(2) INFORMATION FOR SEQ ID NO:82:	
15	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
20	(2) 101020011 111001	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:	
25	TGGGATCCGA GAAGTCTATA TCCCATC	27
	(2) INFORMATION FOR SEQ ID NO:83:	
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:	
	TGGGATCCTT AGAAGTCTAT ATCCCATC	28
40	(2) INFORMATION FOR SEQ ID NO:84: (i) SEQUENCE CHARACTERISTICS:	
45	(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:	
50	GTCTCGAGCC ATGAACGCCC CCGAGCGG	28
	(2) INFORMATION FOR SEQ ID NO:85:	
55	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid	
		186

	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:	-
	GTGAATTCTC GTCTGATTTC TGGCAGGAGG	30
10	(2) INFORMATION FOR SEQ ID NO:86:	
15	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:	
20	GTGAATTCTT TACGTCTGAT TTCTGGCAGG	30
	(2) INFORMATION FOR SEQ ID NO:87:	
25	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 34 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
30		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:	·
	GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC	34
35	(2) INFORMATION FOR SEQ ID NO:88:	
40	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:	
45	GTGGATCCAA GGAGCTGATC TGACTCAGCA G	31
	(2) INFORMATION FOR SEQ ID NO:89:	
50 55	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:	
	GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG	32
5	(2) INFORMATION FOR SEQ ID NO:90:	
10	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:	
	CCTCCTAAGC TTATCATGGA CCATTATGAT TC	32
	(2) INFORMATION FOR SEQ ID NO:91:	
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	
25	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:	
30	CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG	33
30	(2) INFORMATION FOR SEQ ID NO:92:	
35	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 45 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG	45
45	(2) INFORMATION FOR SEQ ID NO:93:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 45 base pairs(B) TYPE: nucleic acid	
50	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:	
55	GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTTC TTCCC	45
		188

	(2) INFORMATION FOR SEQ ID NO:94:	
5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 29 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:	
	GGGAAGCTTC CATGAGCGAG ACGGTCATC	29
15	(2) INFORMATION FOR SEQ ID NO:95:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid	
20	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(2, 20002002, 220002	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:	• •
25	CCCGGATCCT CAGGGAGAAC CCCGCTTC	28
	(2) INFORMATION FOR SEQ ID NO:96:	
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:	
	GTGAATTCGA CCATGGAGCG GCCCCCGGGG	30
40	(2) INFORMATION FOR SEQ ID NO:97:	
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs	
45	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:	
30	GTGGTACCCA TTCTGTTAAC CAACTCC	27
	(2) INFORMATION FOR SEQ ID NO:98:	
55	(i) SEQUENCE CHARACTERISTICS:	•
. 4	(A) LENGTH: 28 base pairs	189

	190	
	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	•
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:	
	GTGGTACCTC ATTCTGTTAA CCAACTCC	28
10	(2) INFORMATION FOR SEQ ID NO:99:	
15	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:	
20	GTCTCGAGAG ATGCTGTCCC GTGGGTGG	28
	(2) INFORMATION FOR SEQ ID NO:100:	
25	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	
30	(D) TOPOLOGY: linear	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:	
35	GTGAATTCGC TTCCTCTTGA GGGAACC	27
	(2) INFORMATION FOR SEQ ID NO:101:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs	
40	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:	
	GTGAATTCAC TTCCTCTTGA GGGAACC	27
50	(2) INFORMATION FOR SEQ ID NO:102:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 29 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	
55	(D) TOPOLOGY: linear	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:	
_	GTCTCGAGCC ATGGAGAACT TCCAAAAGG	29
5	(2) INFORMATION FOR SEQ ID NO:103:	
10	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:	
	GTGGATCCCA GAGTCGAAGA TGGGGTAC	28
20	(2) INFORMATION FOR SEQ ID NO:104:	
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 29 base pairs(B) TYPE: nucleic acid	
25	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	÷.
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:	
30	GTGGATCCTC AGAGTCGAAG ATGGGGTAC	29
	(2) INFORMATION FOR SEQ ID NO:105:	:
35	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:	
	GTGAATTCGG CGATGCCAGA CCCCGCGGCG	30
45	(2) INFORMATION FOR SEQ ID NO:106:	
50	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid	
50	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
5 5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:	
JJ	GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC	32 19

PCT/DK98/00145

	(2) INFORMATION FOR SEQ ID NO:107:	
5	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:	
	GTGGATCCTC AGGCACAGGC AGCCTCAGCC TTC	33
15	(2) INFORMATION FOR SEQ ID NO:108:	
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 2616 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
25	(ii) MOLECULE TYPE: cDNA(ix) FEATURE:(A) NAME/KEY: Coding Sequence(B) LOCATION: 12613(D) OTHER INFORMATION:	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:	
35	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15	48
30	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30	96
40	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 40 45	144
45	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60	192
50	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 75 80	240
55	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288
	CGC ACC ATC TTC TAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG	336 192

	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	
5					GGC Gly												384
10					GAG Glu												432
45					CAC His												480
15					AAC Asn 165										_		528
20					GAC Asp												576
25					CCC Pro												624
30					AAC Asn												672
35					GGG Gly											TCC Ser 240	720
33					CGA Arg 245												768
40					CCC Pro												816
45					AAG Lys												864
50					CGC Arg												912
					CAC His												960
55	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG	GCA	GAG	CTC	TGC	1008

										194							
	Tyr	Ala	ı Ile	: Ala	Gly 325		Lys	Ala	His	Cys 330		Pro	Ala	Glu	Leu 335	_	
5	GAG Glu	TTC Phe	TAC Tyr	TCG Ser 340	Arg	GAC Asp	CCC Pro	GAC Asp	GGG Gly 345	Leu	CCC	TGC Cys	AAC Asn	CTG Leu 350	CGC Arg	AAG Lys	1056
10	CCG Pro	TGC Cys	AAC Asn 355	Arg	CCG Pro	TCG Ser	GGC Gly	CTC Leu 360	Glu	CCG Pro	CAG Gln	CCG Pro	GGG Gly 365	GTC Val	TTC Phe	GAC Asp	1104
15	TGC Cys	CTG Leu 370	Arg	GAC Asp	GCC Ala	ATG Met	GTG Val 375	CGT Arg	GAC Asp	TAC Tyr	GTG Val	CGC Arg 380	CAG Gln	ACG Thr	TGG Trp	AAG Lys	1152
	CTG Leu 385	GAG Glu	GGC Gly	GAG Glu	GCC Ala	CTG Leu 390	GAG Glu	CAG Gln	GCC Ala	ATC Ile	ATC Ile 395	AGC Ser	CAG Gln	GCC Ala	CCG Pro	CAG Gln 400	1200
20	GTG Val	GAG Glu	AAG Lys	CTC Leu	ATT Ile 405	GCT Ala	ACG Thr	ACG Thr	GCC Ala	CAC His 410	GAG Glu	CGG Arg	ATG Met	CCC Pro	TGG Trp 415	TAC Tyr	1248
25	CAC His	AGC Ser	AGC Ser	CTG Leu 420	ACG Thr	CGT Arg	GAG Glu	GAG Glu	GCC Ala 425	GAG Glu	CGC Arg	AAA Lys	CTT Leu	TAC Tyr 430	TCT Ser	GGG Gly	1296
30	GCG Ala	CAG Gln	ACC Thr 435	GAC Asp	GGC Gly	AAG Lys	TTC Phe	CTG Leu 440	CTG Leu	AGG Arg	CCG Pro	CGG Arg	AAG Lys 445	GAG Glu	CAG Gln	GGC Gly	1344
35	ACA Thr	TAC Tyr 450	GCC Ala	CTG Leu	TCC Ser	CTC Leu	ATC Ile 455	TAT Tyr	GGG Gly	AAG Lys	ACG Thr	GTG Val 460	TAC Tyr	CAC His	TAC Tyr	CTC Leu	1392
	ATC Ile 465	AGC Ser	CAA Gln	GAC Asp	AAG Lys	GCG Ala 470	GGC Gly	AAG Lys	TAC Tyr	TGC Cys	ATT Ile 475	CCC Pro	GAG Glu	GGC Gly	ACC Thr	AAG Lys 480	1440
40	TTT Phe	GAC Asp	ACG Thr	CTC Leu	TGG Trp 485	CAG Gln	CTG Leu	GTG Val	GAG Glu	TAT Tyr 490	CTG Leu	AAG Lys	CTG Leu	AAG Lys	GCG Ala 495	GAC Asp	1488
45	GGG Gly	CTC Leu	ATC Ile	TAC Tyr 500	TGC Cys	CTG Leu	AAG Lys	GAG Glu	GCC Ala 505	TGC Cys	CCC Pro	AAC Asn	AGC Ser	AGT Ser 510	GCC Ala	AGC Ser	1536
50	AAC Asn	GCC Ala	TCA Ser 515	GGG Gly	GCT Ala	GCT Ala	GCT Ala	CCC Pro 520	ACA Thr	CTC Leu	CCA Pro	GCC Ala	CAC His 525	CCA Pro	TCC Ser	ACG Thr	1584
55	TTG Leu	ACT Thr 530	CAT His	CCT Pro	CAG Gln	AGA Arg	CGA Arg 535	ATC Ile	GAC Asp	ACC Thr	CTC Leu	AAC Asn 540	TCA Ser	GAT Asp	GGA Gly	TAC Tyr	1632
	ACC	CCT	GAG	CCA	GCA	CGC	ATA	ACG	TCC	CCA	GAC	AAA	CCG	CGG	CCG	ATG	1680

	Thr 545	Pro	Glu	Pro	Ala	Arg 550	Ile	Thr	Ser	Pro	Asp 555	Lys	Pro	Arg	Pro	Met 560	
5					AGC Ser 565												1728
10					AAG Lys		_								_	_	1776
15					GGC Gly												1824
13					AAG Lys												1872
20	_	_			AAG Lys												1920
25					CTG Leu 645				-		-						1968
30		_	_		GCC Ala				_		_		_	_	_	_	2016
35					TTC Phe												2064
33					CTG Leu												2112
40					TTT Phe												2160
45					CAC His 725												2208
50					GAC Asp												2256
					TGG Trp												2304
55	TCC	AGC	CGC	AGC	GAT	GTC	TGG	AGC	TAT	GGG	GTC	ACC	ATG	TGG	GAG	GCC	2352

	Ser	Ser 770	Arg	Ser	Asp	Val	Trp 775	Ser	Tyr	Gly	Val	Thr 780	Met	Trp	Glu	Ala	
5		TCC Ser															2400
10		GCC Ala															2448
15		CCC Pro	- '				-					. – –					2496
15		GAT Asp															2544
20		TAC Tyr 850															2592
25		GCT Ala						TGA									2616
30		(i	(A) (B)	INE EQUEN LENC TYPE STR	ICE (STH: E: an	CHARA 871 nino	CTEF amir acio	RISTI no ac	CS:	NO: 1	109:						
35			i) N	TOPO OLEO SAGMI	CULE	TYPE	E: pr	otei						•			
40		()	(i) S	EQUE	ENCE	DESC	RIPT	NOI:	SE(Q ID	NO: 1	109:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu	
45		Glu	Leu	Asp 20	-	Asp	Val	Asn	Gly 25		Lys	Phe	Ser	Val 30		Gly	
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
50	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80	
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
55	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	qaA	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	

			115					120					125			
	Ile	Asp 130		Lys	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
5	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
10	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
15	225				Gly	230			_		235					240
	-		_		Arg 245					250					255	
				260	Pro				265					270		
20			275		Lys			280			_		285			
	_	290			Arg		295					300				
25	305				His	310					315					320
	_				Gly 325 Arg					330					335	
30			_	340	Pro				345					350		
30		-	355	_	Ala			360					365			
	-	370	_	_	Ala		375					380				
35	385				Ile	390					395					400
			_		405 Thr					410					415	
40				420					425					430		Gly
			435					440					445			Leu
		450			Lys		455					460				•
45	465			_	Trp	470					475					480
		_			485 Cys					490					495	
50				500	Ala				505					510		
			515	_	Gln			520					525			
		530			Ala		535					540				
5 5	545 Pro	Met	Asp	Thr	Ser	550 Val	Tyr	Glu	Ser	Pro	555 Tyr	Ser	Asp	Pro	Glu	560 Glu

					565					570					575	
		Lys		580					585					590		
5	Asp	Ile	Glu 595	Leu	Gly	Cys	Gly	Asn 600	Phe	Gly	Ser	Val	Arg 605	Gln	Gly	Val
	Tyr	Arg 610	Met	Arg	Lys	Lys	Gln 615	Ile	Asp	Val	Ala	Ile 620	Lys	Val	Leu	Lys
	Gln 625	Gly	Thr	Glu	Lys	Ala 630	Asp	Thr	Glu	Glu	Met 635	Met	Arg	Glu	Ala	Gln 640
10	Ile	Met	His	Gln	Leu 645	Asp	Asn	Pro	Tyr	Ile 650	Val	Arg	Leu	Ile	Gly 655	Val
	_	Gln		660					665					670		
15		Leu	675					680					685			
		Val 690					695					700				
	Glu 705	Glu	Lys	Asn	Phe	Val 710	His	Arg	Asp	Leu	Ala 715	Ala	Arg	Asn	Val	Leu 720
20	Leu	Val	Asn	Arg	His 725	Tyr	Ala	Lys	Ile	Ser 730	Asp	Phe	Gly	Leu	Ser 735	Lys
	Ala	Leu	Gly	Ala 740	Asp	Asp	Ser	Tyr	Tyr 745	Thr	Ala	Arg	Ser	Ala 750	Gly	Lys
25	Trp	Pro	Leu 755	Lys	Trp	Tyr	Ala	Pro 760	Glu	Cys	Ile	Asn	Phe 765	Arg	Lys	Phe
	Ser	Ser 770	Arg	Ser	Asp	Val	Trp 7 7 5	Ser	Tyr	Gly	Val	Thr 780	Met	Trp	Glu	Ala
	Leu 785	Ser	Tyr	Gly	Gln	Lys 790	Pro	Tyr	Lys	Lys	Met 795	Lys	Gly	Pro	Glu	Val 800
30	Met	Ala	Phe	Ile	Glu 805	Gln	Gly	Lys	Arg	Met 810	Glu	Cys	Pro	Pro	Glu 815	Cys
	Pro	Pro	Glu	Leu 820	Tyr	Ala	Leu	Met	Ser 825	Asp	Cys	Trp	Ile	Tyr 830	Lys	Trp
35	Glu	Asp	Arg 835	Pro	Asp	Phe	Leu	Thr 840	Val	Glu	Gln	Arg	Met 845	Arg	Ala	Cys
	Tyr	Tyr 850	Ser	Leu	Ala	Ser	Lys 855	Val	Glu	Gly	Pro	Pro 860	Gly	Ser	Thr	Gln
	Lys 865	Ala	Glu	Ala	Ala	Cys 870	Ala									
40			(2)	INI	FORM	OITA	N FOI	R SE	Q ID	NO:	110:					
		(-	i) SI	OHE	ICE (מממי	ישרט	ንፐርጥ	rcs ·							
		(-	(A)	LENG	TH:	2598	B bas	se pa								
45					E: nu ANDEI				e							
			(D)	TOP	OLOGY	Y: 1:	inea	ר								
50			ii) N ix) N		CULE JRE:	TYP	E: cl	ANC								
			(A)	IAN (ME/KI	EY: (Codi	ng Se	eguei	nce						
			(B)	LO	CATIO	ON: 3	1:	2595	-							
55		(-			ENCE				· SF	חז כ	МΟ٠	110.				
		\-	/					14		2 10						

5			GCG Ala 5							48
Ü			GAG Glu							96
10			CGC Arg							144
15			GAT Asp							192
20			TAC Tyr							240
25			GAG Glu 85							288
			CCG Pro							336
30			TGC Cys					_		384
35			CTG Leu							432 ·
40			GTG Val							480
45			CAC His 165							528
			GCG Ala							576
50			ACA Thr						_	624
55			ATC Ile							672

5	_	_							TAT Tyr		720
									TGC Cys		768
10									CTC Leu 270		816
15									ACC Thr		864
20									CCA Pro		912
25									CCC Pro		960
									CGC Arg		1008
30									GGC Gly 350		1056
35									GTG Val		1104
40					Glu	Ala	Asp	Thr	GAG Glu		1152
45									ATC Ile		1200
									ATG Met		1248
50									AGG Arg 430		1296
55									TCC Ser		1344

201

5					GAG Glu									_	1392
0					GTT Val 470										1440
10					CTG Leu										1488
15					CCG Pro										1536
20					AGC Ser										1584
25					TCC Ser										1632
					GCC Ala 550								_		16.80
30					CCC Pro										1728
35					GAT Asp										1776
40		Ala	Cys	Tyr	TAC Tyr	Ser	Leu	Ala	Ser	Lys	Glu	Gly			1824
45					GCT Ala										1872
					AAG Lys 630										1920
50					GAC Asp										1968
55					GGC Gly										2016

202

5			ACC Thr							_	2064
J			ACC Thr								2112
10			CAC His								2160
15			ACC Thr						_		2208
20			AAG Lys 740								2256
25			GAC Asp								2304
			TAC Tyr							_	2352
30			ATC Ile								2400
35			CAG Gln								2448
40			GTG Val 820								2496
45			AAA Lys							CTG Leu	2544
			 ACC Thr	 	 	 					2592
50	AAG Lys 865	TAA									2598

55 (2) INFORMATION FOR SEQ ID NO:111:

203

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 865 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

	Met 1	Pro	Asp	Pro	Ala 5	Ala	His	Leu	Pro	Phe 10	Phe	Tyr	Gly	Ser	Ile 15	Ser
15	Arg	Ala	Glu	Ala 20	Glu	Glu	His	Leu	Lys 25	Leu	Ala	Gly	Met	Ala 30	Asp	Gly
			35					40					45	Tyr		
		50			_		55					60		Glu	_	
20	Leu 65	Asn	Gly	Thr	Tyr.	Ala 70	Ile	Ala	Gly	Gly	Lys 75	Ala	His	Cys	Gly	Pro 80
					85		-		_	90			_	Leu	95	
25				100					105					Pro 110		
			115	_	_			120					125	Tyr		_
20		130	_	-			135					140		Ile		
30	145					150	•				155			His		160
			_	-	165					170				Glu	175	_
35		-		180				-	185	-				Arg 190		_
			195			_		200				-	205	Lys		
40	_	210	_				215	_	_		_	220	-	Cys		
40	225			_		230			_		235			Tyr		240
					245					250				Cys	255	
45				260				_	265					Leu 270		
			275					280					285	Thr		
50		290					295					300		Pro		
	305			• • •	-	310	,				315			•		320 Asn
					325			_		330				Gly	335	
55				340					345					350 Val		
	Arg	0111	CTA	Val	- y -	AT 9	1.100	Ar 9	БÃЗ	шуз	O 111	x 1 C	r25	val	nia	

			355					360					365			
	Lys	Val		Lys	Gln	Gly	Thr		Lys	Ala	Asp	Thr		Glu	Met	Met
	•	370		•		•	375		•		•	380				
	Arg	Glu	Ala	Gln	Ile	Met	His	Gln	Leu	Asp	Asn	Pro	Tyr	Ile	Val	Arg
5	385					390					395					400
	Leu	Ile	Gly	Val		Gln	Ala	Glu	Ala		Met	Leu	Val	Met		Met
		~ 3	~1	~ 7	405			_	_,	410			_	_	415	~3
	Ala	Gly	GTA	420	Pro	Leu	HIS	гуѕ	Pne 425	ьeu	val	GIA	ьуs	Arg	GIU	GIU
10	Tle	Pro	Val		Asn	Val	Ala	Glu		Leu	His	Gln	Val		Met	Glv
.0	110	110	435	001		141		440	Deu	пси	1123	0111	445	501		O _T
	Met	Lys	Tyr	Leu	Glu	Glu	Lys	Asn	Phe	Val	His	Arg	Asp	Leu	Ala	Ala
		450					455					460				
	_	Asn	Val	Leu	Leu		Asn	Arg	His	Tyr		ГÀг	Ile	Ser	Asp	
15	465	T	0	T	71-	470	a1	71-	3	3	475			77 la	77-	480
	GIY	Leu	ser	ьуs	485	Leu	GIA	АТА	Asp	490	ser	Tyr	Tyr	Thr	495	Arg
	Ser	Ala	Glv	Lvs		Pro	Leu	Lvs	Trp		Ala	Pro	Glu	Cvs		Asn
			1	500	<u>F</u>			-1-	505	-1-				510		
20	Phe	Arg	Lys	Phe	Ser	Ser	Arg	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Val	Thr
			515					520					525			
	Met	Trp	Glu	Ala	Leu	Ser		Gly	Gln	Lys	Pro	-	Lys	Lys	Met	Lys
	0 3	530	a 1	77-7		21-	535	- 1-	~ 1	~1	~ 1	540			01	G
25	545	Pro	GIU	vaı	мес	550	Pne	TTE	GIU	GIN	555	rys	Arg	мес	GIU	560
23		Pro	Glu	Cvs	Pro		Glu	Len	Tvr	Δla		Met	Ser	Asn	Cvs	
				C J D	565	110	0.10		- 7 -	570	LCu		001		575	
	Ile	Tyr	Lys	Trp	Glu	Asp	Arg	Pro	Asp	Phe	Leu	Thr	Val	Glu	Gln	Arg
				580					585					590		
30	Met	Arg		Cys	Tyr	Tyr	Ser		Ala	Ser	Lys	Val		Gly	Pro	Pro
	a 1	G	595	91	T	77-	a 1	600		a			605	D	D	11- 1
	GIY	Ser 610	inr	GIII	гÀг	Ата	615	Ата	Ата	Cys	Ата	620	Asp	PIO	PLO	Vai
	Ala	Thr	Met	Val	Ser	Lvs		Glu	Glu	Leu	Phe		Glv	Val	Val	Pro
35	625					630	1				635		1			640
	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val
					645					650					65 5	
	Ser	Gly	Glu	_	Glu	Gly	Asp	Ala		Tyr	Gly	Lys	Leu		Leu	Lys
40	Dho	т10	Crra	660	Thr	C111	Tira	T 033	665	17 - 1	Dwo	Tree.	Dwa	670	T 011	Val
40	PHE	116	675	1111	1111	Gry	пур	680	PLO	vai	PIO	пр	685	Lill	neu	vaı
	Thr	Thr		Thr	Tyr	Gly	Val		Cys	Phe	Ser	Arq		Pro	Asp	His
		690			-	•	695		- 1			700	4		-	
	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val
45	705					710					715					720
	Gln	Glu	Arg	Thr		Phe	Phe	Lys	Asp	_	Gly	Asn	Tyr	Lys		Arg
	λιο	Glu	Wa l	Lvc	725 Dhe	Clu	Cly	Λαρ	Thr	730	v. l	Λαn	λκα	Tlo	735	T.GII
	AIA	GIU	vai	740	FIIC	Giu	GIY	Asp	745	Leu	vaı	MSII	Arg	750	Gru	пец
50	Lys	Gly	Ile		Phe	Lvs	Glu	Asp		Asn	Ile	Leu	Glv		Lys	Leu
	•	4	755	-		-		760	4			_	765		-	
	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln
	_	770			_		775	•	_		_	780	_			_
55		Asn	GLY	Ile	гуѕ	Val 790	Asn	Phe	Lys	Ile	_	His	Asn	Ile	GLu	
55	785 Glv	Ser	Va 1	Gln	Len		Δen	Wie	Three	G15	795 Gln	Acr	Thr	Dro	Tle	800 Glv
	1						٦ي		- y -		O 1 11		- 41J	0		~ _ y

	Asp C	Gly	Pro	Val 820	805 Leu	Leu	Pro	Asp	Asn 825	810 His	Tyr	Leu	Ser	Thr 830	815 Gln	Ser		
5	Ala I	Leu	Ser 835		Asp	Pro	Asn	Glu 840		Arg	Asp	His	Met 845		Leu	Leu		
Ü	Glu E	Phe 350		Thr	Ala	Ala	Gly 855		Thr	Leu	Gly	Met 860		Glu	Leu	Tyr		
10	Lys 865																	
10			(2)	INE	FORMA	ATION	1 FOF	R SEÇ	Q ID	NO: 1	L12:							
15		(i	(A) (B) (C)	LENG TYPE STRA	TH: : nu ANDEI	1635 uclei ONESS	bas cac	ingle	airs									
20		-		OLEC EATU		TYPE	E: cI	ONA										
								ng Se	equer	ice								
25							L1 RMATI											
		(x	i) S	EQUE	ENCE	DESC	CRIPT	CION:	: SE(Q ID	NO: 1	112:						
30	ATG C																48	
	GTT C																96	
35			•	20		J		•	25		-			30				
	AAG A Lys I	Lys	_													GCC Ala	. 144	
40	ATC C																192	
45	AAG C Lys I 65																240	
50	GAA T																288	-
	ACT C																336	
55	CAG (GGC	CTA		TTC	TGC	CAT	TCT		CGG	GTC	CTC	CAC		GAC	CTT	384	205

	Gln	Gly	Leu 115	Ala	Phe	Cys	His	Ser 120	His	Arg	Val	Leu	His 125	Arg	Asp	Leu ·		
5													ATC Ile			_	432	
10													CGT Arg				480	
45													ATC Ile				528	
15													CTG Leu				576	
20													GGA Gly 205				624	
25													ACC Thr				672	
30													AAG Lys				720	
													CCT Pro				768	
35													TAC Tyr				816	
40													TTC Phe 285				864	
45													CCA Pro				912	
50													GTG Val				960	
						Gly					His		TTC Phe				1008	
55	GGC	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	1056	206

207

									-									
	Gly	Glu	Gly	Glu 340	Gly	Asp	Ala	Thr	Tyr 345	Gly	Lys	Leu	Thr	Leu 350	Lys	Phe		
	ATC	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC		1104
5		Cys																
			355					360					365					
	א כיכי	CTG	אככ	TAC	CCC	стс	CNG	тсс	ጥጥር	»GC	CGC	TAC	כככ	GAC	CAC	ATG		1152
		Leu																
10		370		-1 -	1		375	1				380		-				
														m. a	ama	an a		1200
		CAG Gln																1200
	385	GIII	urs	Asp	FIIC	390	цуз	JCI	Ala	rice	395	014	Cry	- 1 -		400		
15																		
		CGC																1248
	Glu	Arg	Thr	Ile	Phe 405	Phe	Lys	Asp	Asp	G1y 410	Asn	Tyr	ràs	Thr	415	Ala		
					402					410								
20		GTG																1296
	Glu	Val	Lys		Glu	Gly	Asp	Thr		Val	Asn	Arg	Ile		Leu	Lys		
				420					425					430				
	GGC	ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG		1344
25	Gly	Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly		Lys	Leu	Glu		
			435					440					445					
	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	GAC	AAG	CAG	AAG		1392
		Asn																
30		450					455					460					,	
	ልልሮ	GGC	ΔΤΓ	ΔΔG	GTG	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC		1440
		Gly																-
	465					470					475					480		
35	7.00	GTG	an a	cmc	ccc	C	CAC	TAC	CNG	CAG	አአሮ	۸۵۵	CCC	ልጥር	GGC	GAC		1488
		Val																2.00
					485			•		490					495			
40	~~~	aa-	ome	ama	ama	000	a	n n ~	ar a	TIN C	ama	700	אממ	CAC	TCC	GCC		1536
40		CCC Pro																1330
	Gry	110	Vul	500	Deu		···		505	- 7 -				510				
																~~~		7.504
15		AGC Ser																1584
45	Leu	ser	515	Asp	PLO	ASII	GIU	520	Arg	Asp	UTS	MEC	525	пец	дси	Olu		
																AAG	Т	1633
50	Phe	Val	Thr	Ala	Ala	Gly			Leu	Gly	Met	Asp 540	Glu	ьeu	Tyr	ьys		
50		530					535					240						
	AA																	1635

(2) INFORMATION FOR SEQ ID NO:113:

55

(i) SEQUENCE CHARACTERISTICS:

PCT/DK98/00145 WO 98/45704

208

(A) LENGTH: 544 amino acids

- (B) TYPE: amino acid (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

5

- (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113: 10

10																
	Met 1	Glu	Asn	Phe	Gln 5	Lys	Val	Glu	Lys	Ile 10	Gly	Glu	Gly	Thr	Tyr 15	Gly
	Val	Val	Tyr	Lys 20	Ala	Arg	Asn	Lys	Leu 25	Thr	Gly	Glu	Val	Val 30	Ala	Leu
15	Lys	Lys	Ile 35	Arg	Leu	Asp	Thr	Glu 40	Thr	Glu	Gly	Val	Pro 45	Ser	Thr	Ala
		Arg 50					55					60				
20	65	Leu		_		70					75		_			80
		Phe			85	_		-	_	90		_			95	
<b>~</b> =		Gly		100					105		-			110		
25		Gly	115			_		120					125			
		Pro 130					135					140				
30	-	Phe	GIA	Leu	Ala	Arg 150	Ala	Phe	GIY	Val	155	vai	Arg	Thr	Tyr	160
30	145	Glu	V = 1	U = 1	Thr		Trn	Tur	Λrα	λla		Glu	Tle	Len	T.en	
					165					170					175	
0.5		Lys	_	180					185					190		
35		Ala	195				_	200					205			
		Asp 210					215					220				
40		Val	Trp	Pro	GIÀ		Thr	Ser	Met	Pro	_	Tyr	гуs	Pro	Ser	240
40	225 Pro	Lys	Trn	בומ	Δra	230 Gln	Aen	Dhe	Ser	Lve	235 Val	Val	Pro	Pro	Len	
					245					250					255	
		Asp	_	260					265				_	270		
45	Lys	Arg	11e 275	Ser	Ala	Lys	Ala	Ala 280	Leu	Ala	His	Pro	Phe 285	Phe	Gln	Asp
		Thr 290					295					300				
		Met	Val	Ser	Lys	_	Glu	Glu	Leu	Phe		Gly	Val	Val	Pro	
50	305	**- 7	<b>~</b> 1	<b>.</b> .	_	310	_		_	<b>a</b> .	315	<b>.</b>	D1	<b>a</b>	**- 3	320
	Leu	val	Glu	ьeu	Asp 325	GIY	Asp	Val	Asn	Gly 330	His	Lys	ьие	ser	Va1 335	Ser
	_	Glu		340	_	_			345		_			350		
55	Ile	Cys	Thr 355	Thr	Gly	Lys	Leu	Pro 360	Val	Pro	Trp	Pro	Thr 365	Leu	Val	Thr

	Thr	Leu 370	Thr	Tyr	Gly	Val	Gln 375	Cys	Phe	Ser	Arg	Tyr 380	Pro	Asp	His	Met	
	Lys 385	Gln	His	Asp	Phe	Phe 390	Lys	Ser	Ala	Met	Pro 395	Glu	Gly	Tyr	Val	Gln 400	
5	Glu	Arg	Thr	Ile	Phe 405	Phe	Lys	Asp	Asp	Gly 410	Asn	Tyr	Lys	Thr	Arg 415	Ala	-
	Glu	Val	Lys	Phe 420	Glu	Gly	Asp	Thr	Leu 425	Val	Asn	Arg	Ile	Glu 430	Leu	Lys	
10	Gly	Ile	Asp 435	Phe	Lys	Glu	Asp	Gly 440	Asn	Ile	Leu	Gly	His 445	Lys	Leu	Glu	
	Tyr	Asn 450	Tyr	Asn	Ser	His	Asn 455	Val	Tyr	Ile	Met	Ala 460	Asp	Lys	Gln	Lys	
	Asn 465	Gly	Ile	Lys	Val	Asn 470	Phe	Lys	Ile	Arg	His 475	Asn	Ile	Glu	Asp	Gly 480	
15	Ser	Val	Gln	Leu	Ala 485	Asp	His	Tyr	Gln	Gln 490	Asn	Thr	Pro	Ile	Gly 495	Asp	
	Gly	Pro	Val	Leu 500	Leu	Pro	Asp	Asn	His 505	Tyr	Leu	Ser	Thr	Gln 510	Ser	Ala	
20	Leu	Ser	Lys 515	Asp	Pro	Asn	Glu	Lys 520	Arg	Asp	His	Met	Val 525	Leu	Leu	Glu	
	Phe	Val 530	Thr	Ala	Ala	Gly	Ile 535	Thr	Leu	Gly	Met	Asp 540	Glu	Leu	Tyr	Lys	. •
			(2)	) INE	FORM	OITA	1 FOI	R SE(	Q ID	NO:	114:						
25		(:		EQUE													ø:
			(B)	TYPE	E: nu	ıcle	ic a	cid									-
30				STRA				_	9								``
				MOLE		TYPE	E: cl	ANC									à.
0.5		(:		FEATU			3·	_									·
35			(B	) LOC	CATIO	ои: С	1:	1632	eque	nce							•
				) OTH					C.T.	0 TD	NO.	114					
40	* <b></b>	•		SEQUI						-			CTC	ccc	איזיכי	CTC	48
	Met	GTG Val			Gly					Thr					Ile		40
45	1	ana	CTC.	an a	5	G N G	C.T.A	7 7 C	aaa	10	7 7 CT	mm.c	n.c.c	CTC	15 TCC	ccc	96
45		GAG Glu		Asp					Gly								20
	ar a	GGC	a s a	20	C N TT	ccc	N C C	m v C	25	7 7 C	CTC	N.C.C	CTC		<del>ጥ</del> ም <b>ር</b>	л. Т.С.	144
50		Gly	Glu					Tyr									
	TOO	ACC	35	ccc	እ አ C	CTC	CCC	40 GTG	ccc	TOO	ccc	ልሮሮ		פיזים	ΔCC	ACC	192
55		Thr															172
55		20					ر ر										

						,	210					
									CCC Pro			240
5									GGC Gly			288
10									AAG Lys			336
15									ATC Ile			384
20									CAC His 140			432
20									GAC Asp			480
25									ATC Ile			528
30									CCC Pro		_	576
35									ACC Thr			624
40		Asp	Asn	Glu	Lys	Asp	His	Met	GTC Val 220			672
40									GAG Glu			720
45									AAG Lys			768
50									AGA Arg			816
55									GAC Asp			864

									411					
			AGT Ser											912
5			AAT Asn											96 <u>.</u> 0
10			CTG Leu											1008
15			TCT Ser 340											1056
20			CAG Gln											1104
20			CGA Arg											1152
25			AAG Lys										_	1200
30			ACT Thr											. 1248
35			CTC Leu 420											1296
40	Ser	Leu	GGC Gly	Cys	Ile	Phe	Ala	Glu		Thr	Arg	_		1344
40			GAT Asp											1392
45			CCA Pro											1440
50			CCA Pro											1488
55			CCC Pro 500											1536

									•	212								
								CGG Arg 520										1584
5								ACC Thr								CTC Leu	Т	1633
	GA																	1635
10			(2)	INF	ORMA	TION	J FOF	R SEC	) ID	NO: J	.15:							
15		i)	(A)	LENC		544	amir	RISTI no ac										
					NDEI			ingle	2									
20							_	rotei cerna										
											NO. 1	115.						
		()	(1) 5	EQUE	ENCE	DESC	RIP.	rion:	SEC	ט דר	NO:	115:						
25	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu		
23	_	Glu	Leu	_	-	Asp	Val	Asn			Lys	Phe	Ser			Gly		
	Glu	Gly	Glu	20 Gly	Asp	Ala	Thr	Tyr	25 Gly	Lys	Leu	Thr	Leu	30 Lys	Phe	Ile		
30	Cvs	Thr	35 Thr	Gly	Lvs	Leu	Pro	40 Val	Pro	Trp	Pro	Thr	45 Leu	Val	Thr	Thr		
		50					55	Phe				60						
	65		_	_		70					75					80		
35					85			Ala		90					95			
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu		
	Val	Lys			Gly	Asp	Thr	Leu	Val	Asn	Arg		Glu 125		Lys	Gly		
40	Ile	-	115 Phe	Lys	Glu	Asp	_	120 Asn	Ile	Leu	Gly	His			Glu	Tyr		
	Asn	130 Tyr	Asn	Ser	His	Asn	135 Val		Ile	Met	Ala	140 Asp	Lys	Gln	Lys	Asn		
	145	T10	T 1/0	17-1	λαη	150	Lvc	Tla	λνα	ніс	155	Tla	Glu	Δsn	Glv	160 Ser		
45	_		_		165					170					175			
	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly		
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200		Leu	Ser	Thr	Gln 205	Ser	Ala	Leu		
50	Ser	Lys 210		Pro	Asn	Glu	Lys 215	Arg		His	Met	Val 220	Leu	Leu	Glu	Phe		
		Thr	Ala	Ala	Gly		Thr		Gly	Met			Leu	Tyr	Lys	Ser		
	225 Glv		Ara	Ser	Ara	230 Ala		G] 11	Asn	Phe	235 Gln	Lvs	Val	Glu	Lvs	240 Ile		
55					245					250					255			
	Gly	Glu	Gly	Thr	Tyr	Gly	Val	Val	Tyr	Lys	Ala	Arg	Asn	Lys	Leu	Thr	•	

				260					265					270			
	Gly	Glu	Val		Ala	Leu	Lys	Lys		Arg	Leu	Asp	Thr		Thr	Glu	
	_		275					280					285				
_	Gly		Pro	Ser	Thr	Ala		Arg	Glu	Ile	Ser		Leu	Lys	Glu	Leu	
5	λαη	290	Dro	λen	Ile	Val	295 Lve	T.e.u	T.e.ii	Aen	Va l	300 Tla	Hic	Thr	Glu	Δen	
	305	птъ	PIO	ASII	116	310	шуз	neu	neu	ASP	315	116	nis	1111	Giu	320	
		Leu	Tyr	Leu	Val		Glu	Phe	Leu	His		Asp	Leu	Lys	Lys		
	-		-		325					330		_			335		
10	Met	Asp	Ala		Ala	Leu	Thr	Gly		Pro	Leu	Pro	Leu		Lys	Ser	
	ጥህም	Len	Dhe	340 Gln	Leu	I.e.i	Gln	Gly	345	λΊз	Dhe	Cve	Hic	350	Hie	Ara	
	ryr	neu	355	GIII	Deu	Deu	GIII	360	Deu	AIG	FIIC	Cys	365	361	HILS	Arg	
	Val	Leu	His	Arg	Asp	Leu	Lys	Pro	Gln	Asn	Leu	Leu	Ile	Asn	Thr	Glu	
15		370					375					380					
	_	Ala	Ile	Lys	Leu		qaA	Phe	Gly	Leu		Arg	Ala	Phe	Gly		
	385	W-1	7 ~~	Thr	Tyr	390	uic	C1,,	v-1	17-1	395	Lou	Trn	Tirr	λνα	400 Ala	
	PIO	vai	Arg	1111	405	1111	1115	Giu	Vai	410	1111	пец	ırp	ı yı.	415	A14	
20	Pro	Glu	Ile	Leu	Leu	Gly	Ser	Lys	Tyr	Tyr	Ser	Thr	Ala	Val	Asp	Ile	
				420					425					430			
	Trp	Ser		Gly	Cys	Ile	Phe		Glu	Met	Val	Thr		Arg	Ala	Leu	
	Dhe	Pro	435	Δsn	Ser	Glu	Tle	440 Asp	Gln	T.em	Phe	Δrσ	445 Tle	Phe	Ara	Thr	
25	riic	450	Cly	wob	001	0	455	пор	0111	ncu.	1 110	460					-
	Leu	Gly	Thr	Pro	Asp	Glu	Val	Val	Trp	Pro	Gly	Val	Thr	Ser	Met	Pro	
	465					470				_	475					480	
	Asp	Tyr	Lys	Pro	Ser	Phe	Pro	Lys	Trp	Ala 490	Arg	Gin	Asp	Phe	Ser 495	Lys	••
30	Val	Val	Pro	Pro	485 Leu	Asp	Glu	Asp	Glv		Ser	Leu	Leu	Ser		Met	
				500					505					510			·
	Leu	His	Tyr	Asp	Pro	Asn	Lys	Arg	Ile	Ser	Ala	Lys	Ala	Ala	Leu	Ala	
	77.5 _	D-1-	515	Dh.	<b>03</b> =	N	17 7	520	T	D	***	D	525	T 011	λ ~~~	Lou	
35	Hls	530	Pne	Pne	Gln	Asp	va: 535	Thr	гÀг	Pro	vaı	540	HIS	ьeu	Arg	Leu	
00		220					333					3.0					
			(2)	INI	FORM	OITA	1 FOI	R SE	Q ID	NO:	116:						
		,	٠														
40		(:	•	~	NCE ( GTH:												
40					Ξ: nι				alls								
					ANDEI				<b>e</b>								
			(D)	TOP	DLOG	: 1:	inea	r									
45		,															
45				MOLE FEAT	CULE	LAbi	ਤ: C!	DNA									
		١.	LX)	CEMI	JKB.												
			(A)	IAN (	ME/K	ΞΥ: (	Codi	ng S	equei	nce							
					CATIO												
50			(D)	) OTI	HER :	INFO	RMAT	ION:									
		( :	xi) s	SEOUI	ENCE	DES	CRIP'	TION	: SEG	O ID	NO:	116:					
		( -	·,	2 .			<b></b>										
					GGC												48
55		Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe		Gly	Val	Val	Pro		Leu	
	1				5					10					15		

	GAG Glu									96
5	 GGC Gly								_	144
10	ACC Thr 50									192
15	ACC Thr									240
20	CAC His								_	288
25	 ACC Thr									336
	AAG Lys								_	384
30	GAC Asp 130									432
35	TAC Tyr									480
40	ATC Ile							_		528
45	CAG Gln								_	576
40	GTG Val									624
50	AAA Lys 210									672
55	ACC Thr									720

						TCC Ser						768
5						CTG Leu 265						816
10						CGC Arg						864
15						GTG Val						912
20						GGA Gly						960
25						CAG Gln						1008
						AAG Lys 345						1056 ;
30						GGC Gly						1104
35						GAG Glu						1152
40			Pro	Gly	Asp	TTC Phe	Val	Leu	Ser			1200
45						CCG Pro						1248
						ACA Thr 425						1296
50						CAT His						1344
55						CTG Leu						1392

216

5							CTG Leu		1440
-							GAG Glu		1488
10							CGT Arg 510		1536
15							AAC Asn		1584
20							AGT Ser		1632
25							CAG Gln		1680
							GGC Gly		1728
30							GAG Glu 590		1776
35							CGG Arg		1824
40					 	 	 TAT Tyr		1872
45							TAC Tyr		1920
							ATT Ile		1968
50							GTC Val 670		2016
55							CAG Gln		2064

5	Glu	AGT Ser 690	Leu	Pro	His	Ala	Gly 695	Pro	Ile	Ile	Val	His 700	Cys	Ser	Ala	Gly	2112
	Ile 705	Gly	Arg	Thr	Gly	Thr 710	Ile	Ile	Val	Ile	Asp 715	Met	Leu	Met	Glu	Asn 720	
10		TCC Ser															2208
15		ATG Met													_	_	2256
20		AAG Lys															2304
25		AAG Lys 770															2352
23		AAC Asn												_		_	2400
30		CGC Arg															2448
35		AAG Lys															24 <u>9</u> 6 .
40		GAG Glu				_						TGA					2532
			(2	) INI	FORM	ATIO	N FO	R SE	DI Ç	NO:	117:						
45		(:	(A) (B) (C)	TYPI STR	NCE ( GTH: E: ar ANDE	843 mino ONES	amii acie S: s	no a d ingl	cids								
50			ii) !	MOLE	CULE CULE	TYP	E: p	rote				-					
55	Met	(: Val	·		ENCE Gly								Val	Pro	Ile	Leu	
				_ 1	4								_				- 4

										210						
	1				5					10					15	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
5		Gly	35	_	_			40	_	_			45	_		
	•	Thr 50		_	_		55			_		60				
	65	Thr	_	_		70				_	75					80
10	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
	_	Thr		100		_		-	105		-			110		
15		Lys	115					120					125			
		Asp 130		•			135					140	_			
00	145	Tyr				150					155					160
20	-	Ile	-		165					170					175	
		Gln Val		180					185					190		
25			195					200					205			
		Lys 210 Thr	_				215					220				
30	225	Leu				230					235					240
30	-	Ser	_		245					250					255	
		Ser	_	260					265					270		
35	_		275			_		280					285			Asn
		290					295					300				Leu
40	305	_				310					315					320 Asp
					325	_	_			330					335	Asp
	_	_		340					345					350		Ala
45	Glu	Thr	355 Leu	Leu	Gln	Ala	Lys	360 Gly	Glu	Pro	Trp	Thr	365 Phe	Leu	Val	Arg
	Glu	370 Ser	Leu	Ser	Gln	Pro	375 Gly	Asp	Phe	Val	Leu	380 Ser	Val	Leu	Ser	Asp
50	385 Gln	Pro	Lys	Ala	Gly	390 Pro	Gly	Ser	Pro	Leu	395 Arg	Val	Thr	His	Ile	400 Lys
					405					410					415	Phe
	Asp	Ser	Leu	420 Thr	Asp	Leu	Val	Glu	425 His	Phe	Lys	Lys	Thr	430 Gly		Glu
55	Glu	Ala	435 Ser	Gly	Ala	Phe	Val	440 Tyr	Leu	Arg	Gln	Pro	445 Tyr		Ala	Thr

		450					455					460				
	465					470			Asn		475					480
5	Lys	Gln	Glu	Ser	Glu 485	Asp	Thr	Ala	Lys	Ala 490	Gly	Phe	Trp	Glu	Glu 495	Phe
	Glu	Ser	Leu	Gln 500	Lys	Gln	Glu	Val	Lys 505	Asn	Leu	His	Gln	Arg 510	Leu	Glu
	_		515					520	Lys				525			
10		530					535		Leu			540				
	545					550			Asn		555					560
15	_				565				Tyr	570					575	
				580		_		_	Gln 585			_		590		
			595					600	Glu				605			
20	-	610		-			615		Gly			620				
	625					630			His		635					640
25					645				Asp	650					655	
		_		660		_			Trp 665					670		
			675					680	Leu				685			
30		690					695		Ile			700				
	705					710			Val		715					720
35					725				Asp	730					735	
				740					Gly 745					750		
	-		755		_			760	Ala				765			
40	-	770					775		Gln	_	_	780				
	785					790			Met		795					800
45					805				Glu	810					815	
				820					Val 825			Gln	Arg	Ser 830	Ala	Asp
	Lys	Glu	Lys 835	Ser	Lys	Gly	Ser	Leu 840	Lys	Arg	Lys					
EΛ																

## (2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2562 base pairs
- (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single

220

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE: 5 (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...2559 (D) OTHER INFORMATION: 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118: ATG CTG TCC CGT GGG TGG TTT CAC CGA GAC CTC AGT GGG CTG GAT GCA 48 Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala 1 10 15 GAG ACC CTG CTC AAG GGC CGA GGT GTC CAC GGT AGC TTC CTG GCT CGG 96 Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg 20 20 CCC AGT CGC AAG AAC CAG GGT GAC TTC TCG CTC TCC GTC AGG GTG GGG 144 Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly 40 GAT CAG GTG ACC CAT ATT CGG ATC CAG AAC TCA GGG GAT TTC TAT GAC 192 25 Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp CTG TAT GGA GGG GAG AAG TTT GCG ACT CTG ACA GAG CTG GTG GAG TAC 240 Leu Tyr Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr 30 75 TAC ACT CAG CAG GGT GTC CTG CAG GAC CGC GAC GGC ACC ATC ATC 288 Tyr Thr Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile 85 90 35 CAC CTC AAG TAC CCG CTG AAC TGC TCC GAT CCC ACT AGT GAG AGG TGG His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp 100 40 TAC CAT GGC CAC ATG TCT GGC GGG CAG GCA GAG ACG CTG CTG CAG GCC 384 Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala 115 AAG GGC GAG CCC TGG ACG TTT CTT GTG CGT GAG AGC CTC AGC CAG CCT 432 45 Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro 130 135 GGA GAC TTC GTG CTT TCT GTG CTC AGT GAC CAG CCC AAG GCT GGC CCA 480 Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro 50 150 GGC TCC CCG CTC AGG GTC ACC CAC ATC AAG GTC ATG TGC GAG GGT GGA 528

220

576

175

Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly

CGC TAC ACA GTG GGT GGT TTG GAG ACC TTC GAC AGC CTC ACG GAC CTG

170

165

	Arg	Tyr	Thr	Val 180	Gly	Gly	Leu	Glu	Thr 185	Phe	Asp	Ser	Leu	Thr 190	Asp	Leu		
5					AAG Lys												624	
10					CAG Gln												672	
15					GTG Val												720	
15					GGC Gly 245												768	
20					TTG Leu										_		816	
25					CGC Arg												864	
30					GGA Gly												912	
25					ATC Ile											_	960	
35					GCC Ala 325												1008	
40					GCG Ala												1056	
45					GAG Glu												1104	
50					CAG Gln												1152	
5.5			_		ACA Thr												1200	
55	CCG	CTG	GAC	AAT	GGA	GAC	CTG	ATT	CGG	GAG	ATC	TGG	CAT	TAC	CAG	TAC	1248	221

	Pro	Leu	Asp	Asn	Gly 405	Asp	Leu	Ile	Arg	Glu 410	Ile	Trp	His	Tyr	Gln 415	Tyr	
5					GAC Asp												1296
10					CAG Gln												1344
15					GTG Val												1392
13					GAC Asp												1440
20					GAC Asp 485												1488
25					GTG Val												1536
30					TTC Phe										_		1584
25					GGC Gly												1632
35					AAT Asn												1680
40					GTG Val 565												1728
45					AAG Lys												1776
50					AAG Lys												1824
55					GCC Ala												1872
33	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	1920

	Gly 625	Val	Val	Pro	Ile	Leu 630	Val	Glu	Leu	Asp	Gly 635	Asp	Val	Asn	Gly	His 640		
5														TAC Tyr			1968	
10														GTG Val 670			2016	
15														TTC Phe			2064	
15														GCC Ala			2112	
20														GAC Asp			2160	
25														CTG Leu			2208	
30														AAC Asn 750			2256	
0.5														TAT Tyr	_		2304	
35														ATC Ile			2352	
40														CAG Gln			2400	٠
45														CAC His			2448	
50							_							CGC Arg 830			2496	
														CTC Leu			2544	
55	GAC	GAG	CTG	TAC	AAG	TAA											2562	223

224

Asp Glu Leu Tyr Lys 850

5 (2) INFORMATION FOR SEQ ID NO:119:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 853 amino acids
  - (B) TYPE: amino acid
- 10 (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg 20 25 Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly 40 Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp 25 Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr 70 75 Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile 90 His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp 30 105 Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala 120 Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro 35 135 140 Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro 150 155 Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly 165 170 40 Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu 185 Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe 200 Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp 45 215 Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp 230 235 Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln 250 50 Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn 260 265 Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg 280 Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile 55 300 295 Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala

	305					310					315					320
		Thr	Tyr	Ile	Ala		Gln	Gly	Cys	Leu		Ala	Thr	Val	Asn	
			_		325					330					335	
5	Phe	Trp	Gln	Met 340	Ala	Trp	GIn	Glu	Asn 345	Ser	Arg	Val	Ile	Val 350	Met	Thr
Ü	Thr	Arg	Glu		Glu	Lys	Gly	Arg		Lys	Cys	Val	Pro		Trp	Pro
			355				_	360					365			
	Glu	Val 370	Gly	Met	Gln	Arg	Ala 375	Tyr	Gly	Pro	Tyr	Ser 380	Val	Thr	Asn	Cys
10	Gly	-	His	Asp	Thr	Thr		Tyr	Lys	Leu	Arg		Leu	Gln	Val	Ser
	385					390	_				395			_		400
	Pro	Leu	Asp	Asn	Gly 405	Asp	Leu	Ile	Arg	Glu 410	Ile	Trp	His	Tyr	Gln 415	Tyr
	Leu	Ser	Trp	Pro		His	Gly	Val	Pro		Glu	Pro	Gly	Gly	Val	Leu
15				420	_			_	425	_	_			430		
	Ser	Phe	Leu 435	Asp	Gln	Ile	Asn	Gln 440	Arg	Gln	Glu	Ser	Leu 445	Pro	His	Ala
	Gly	Pro		Ile	Val	His	Cys		Ala	Gly	Ile	Gly		Thr	Gly	Thr
	-	450					455					460			_	
20	Ile 465	Ile	Val	Ile	Asp	Met 470	Leu	Met	Glu	Asn	11e 475	Ser	Thr	Lys	Gly	Leu 480
		Cys	Asp	Ile	Asp		Gln	Lys	Thr	Ile		Met	Val	Arg	Ala	
	_	_			485		_,			490	_	_	_,	3	495	** . 7
25	Arg	Ser	GTÀ	Met 500	Val	GIn	Thr	Glu	A1a 505	GIn	Tyr	Lys	Pne	510	Tyr	vaı
20	Ala	Ile	Ala		Phe	Ile	Glu	Thr		Lys	Lys	Lys	Leu		Val	Leu
		_	515		~1	<b>~</b> 1	~1	520	<b>~</b> 1	<b></b>	<b>0</b> 1		525	mla		Dage
	Gin	530	GIn	гуѕ	GIÀ	GIN	535	ser	GIU	Tyr	GIY	540	TTE	Thr	Tyr	PIO
30	Pro		Met	Lys	Asn	Ala		Ala	Lys	Ala	Ser		Thr	Ser	Ser	Lys
	545	<b>.</b>	<b>a</b> 1	2	17-7	550	<b>~1</b>	7	τ	77.2 <b>-</b>	555	T	7	T	7 ~ ~	560
	HIS	гуѕ	GIU	Asp	565	Tyr	GIU	Asn	ьeu	570	Ini	гуу	ASII	гуs	Arg 575	Giu
	Glu	Lys	Val	Lys	Lys	Gln	Arg	Ser	Ala	Asp	Lys	Glu	Lys		Lys	Gly
35	C 0 25	T 0	T	580	T	7 ~~~	T 1 0	T 011	585	C 0 x	Thr	Wal.	Dro	590	בות	λνα
	ser	ьец	ьув 595	Arg	цуѕ	Arg	TIE	600	GIII	ser	IIII	vai	605	Arg	ATG	Arg
	Asp	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr
40	Clv	610	1/21	Dro	Tle	Len	615 Val	Glu	Len	Λcn	Gly	620	Wa l	Λen	Gly	ніс
70	625	vai	vai	PIO	116	630	vai	Gru	пец	АБР	635	Yaħ	vai	ASII	Gry	640
	Lys	Phe	Ser	Val		Gly	Glu	Gly	Glu	_	Asp	Ala	Thr	Tyr	Gly	Lys
	Len	Thr	Leu	Lve	645	Tle	Cve	Thr	Thr	650	Lve	T.e.u	Pro	Val	655 Pro	Trn
45	Leu	1111	beu	660	FIIC	116	Суз	1111	665	Giy	цуз	пси	110	670	110	
	Pro	Thr		Val	Thr	Thr	Leu		Tyr	Gly	Val	Gln		Phe	Ser	Arg
	Tur	Dro	675	шic	Met	Larg	Gln	680	Agn	Dhe	Dhe	Lve	685 Ser	Δla	Met	Pro
	TYL	690	Asp	1113	Mec	цуз	695	HIS	лар	FIIC	rne	700	JCI	niu	1100	110
50		Gly	Tyr	Vaļ	Gln		Arg	Thr	Ile	Phe		Lys	Asp	Asp	Gly	
	705	Lve	Thr	Δra	Δla	710	Val	Lve	Phe	Glu	715	Asn	Thr	Leu	Val	720 Asn
					725					730					735	
EE	Arg	Ile	Glu		Lys	Gly	Ile	Asp		Lys	Glu	Asp	Gly		Ile	Leu
55	G1v	His	Lvs	740 Leu	Glu	Tvr	Asn	Tvr	745 Asn	Ser	His	Asn	Val	750 Tyr	Ile	Met
	1		_,_			<u> </u>		- 1 <b>-</b>						1 -		

			755					760					765					
	Ala	Asp 770	Lys	Gln	Lys	Asn	Gly 775	Ile	Lys	Val	Asn	Phe 780	Lys	Ile	Arg	His		
5	Asn 785	Ile	Glu	Asp	Gly	Ser 790	Val	Gln	Leu	Ala	Asp 795	His	Tyr	Gln	Gln	Asn 800		
		Pro	Ile	Gly	Asp 805		Pro	Val	Leu	Leu 810		Asp	Asn	His	Tyr 815			
	Ser	Thr	Gln	Ser 820		Leu	Ser	Lys	Asp 825		Asn	Glu	Lys	Arg 830		His		
10	Met	Val	Leu 835		Glu	Phe	Val			Ala	Gly	Ile		Leu	Gly	Met		
	Asp	Glu 850		Tyr	Lys			840					845					
15			(2)	INI	FORM	OITA	1 FOE	R SE(	Q ID	NO:	L20:							
20		i <b>)</b>	(A) (B) (C)	EQUEN LENC TYPE STRA	ETH: E: nu ANDEI	2994 acle: ONES	bas ic ac	se pa cid ingle	airs									
			Li) N	TOPO OLEO EATU	CULE													
25			(A)	NAM LOC	ME/KI	ON: 3	L2	2991	equer	ıce								
30		(2	ci) S	EQUE	ENCE	DESC	CRIP	поп	: SE(	QI Q	NO: 1	120:						
35														CCC Pro			48	
33														GTG Val 30		GGC Gly	96	
40														AAG Lys			144	
45														GTG Val			192	
50														CAC His			240	
55	_													GTC Val			288	
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	226

										221								
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu		
5		AAG Lys															384	
10		GAC Asp 130															432	
		TAC Tyr												_			480	
15		ATC Ile															528	
20		CAG Gln															576	
25		GTG Val															624	
30		AAA Lys 210															672 ·.	
		ACC Thr															720	
35		CTC Leu															768	
40		GGG Gly															816	
45		GGC Gly															864	
50		GAT Asp 290															912	
		AAC Asn															960	
55	AAC	CAT	GCC	AAT	GTT	GTA	AAG	GCC	TGT	GAT	GTT	CCT	GAA	GAA	TTG	AAT	1008	227

228

	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Cys	Asp 330	Val	Pro	Glu	Glu	Leu 335	Asn	
5					GAT Asp												1056
10					AAG Lys										_		1104
4.5					ATA Ile												1152
15					GAA Glu												1200
20					CAG Gln 405												1248
25					GCC Ala												1296
30					CTG Leu												1344
					ACT Thr												1392
35					GGA Gly												1440
40					AAG Lys 485												1488
45					TCA Ser												1536
50					TGT Cys												1584
					AAT Asn			Pro									1632
55	CTT	ACT	TTG	AAG	CAG	CCA	AGA	TGT	TTT	GTA	TTA	ATG	GAT	CAC	ATT	ТТG	1680

	Leu 545	Thr	Leu	Lys	Gln	Pro 550	Arg	Cys	Phe	Val	Leu 555	Met	Asp	His	Ile	Leu 560		
5		TTG Leu															1728	
		TTT Phe		Leu	CCA				Ser	CTT				Gln	TCT		1776	
10	ATT	GAG	CGT	580 GAA	ACT	GGA	ATA	ААТ	585 ACT	GGT	TCT	CAA	GAA	590 CTT	CTT	TCA	1824	
15	Ile	Glu	Arg 595	Glu	Thr	Gly	Ile	Asn 600	Thr	Gly	Ser	Gln	Glu 605	Leu	Leu	Ser		
		ACA Thr 610															1872	
20		GAT Asp															1920	
25		AGT Ser															1968	
30		TGT Cys															2016	
		CAG Gln															2064	
35		AAA Lys 690															2112	
40		AGT Ser		-													2160	
45		ATC Ile															2208	
50		AGC Ser															2256	
		ATA Ile															2304	
55	AAG	GCC		CAC	TAT	GCT	GAG	GTT	GGT	GTC	ATT	GGA	TAC	CTG	GAG	GAT	2352	229

	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp		
5														AAG Lys			2400	
10														CAG Gln			2448	
<b>1</b> E														CAC His 830			2496	
15		-												GTG Val			2544	
20														AAG Lys			2592	
25														GAA Glu			2640	
30														ATG Met			2688	
0.5														TGT Cys 910			2736	
35														GCA Ala			2784	
40														CAT His			2832	
45														TCA Ser			2880	
50														ACT Thr		_	2928	
														CTT Leu 990			2976	
55	AGT	TGG	TTA	ACA	GAA	TGA											2994	230

Ser Trp Leu Thr Glu 995

```
5
               (2) INFORMATION FOR SEQ ID NO:121:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 997 amino acids
              (B) TYPE: amino acid
10
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
15
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:
     Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
     Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
20
                                      25
      Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
                                  40
     Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
25
                              55
      Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
                                              75
     Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                                          90
30
      Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                                      105
      Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
      Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr
35
                              135
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                          150
                                              155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                           170
40
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                      185
                  180
      Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
45
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
      Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro
                                           250
                      245
      Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg
50
                                      265
                                                           270
      Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu
                                                      285
              275
                                  280
      Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr
```

295

Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu

	305					310					315					320
	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Cys	Asp 330	Val	Pro	Glu	Glu	Leu 335	Asn
5				340					345					Cys 350		
	-	-	355	_	_			360	-				365	Cys	-	
	_	370					375				_	380		Ser		
10	385	_				390					395	_		Lys		400
					405					410				Lys	415	
15	_		_	420					425					Cys 430		
			435					440					445	Glu		
20		450					455	_	_			460		Met		
20	465	_				470					475			Gln		480
		_			485					490				Ile	495	
25	-			500		_			505					Leu 510		
			515					520					525	Asn		
30		530					535				_	540	_	Pro		
30	545			_		550	_	_			555		_	His Lys		560
			_		565					570				Gln	575	
35				580					585					590 Leu		
			595					600					605	Gln		
40		610					615					620		Leu		
40	625					630					635			Ser		640
	_		_		645			_		650				Leu	655	
45				660					665					670 Val		
			675					680					685	Ala		
50		690		_	_		695				-	700	-	Lys		
30	705					710					715			Phe		720
					725				-	730	_			Met	735	
55				740					745					750 Met		
	~ ~ ~	T T T	$\neg = \bot$		-	y	1.1	40.1	-10				-1		~ 44	بايدب

			755					760					765						
	Lys	Ala 770		His	Tyr	Ala	Glu 775		Gly	Val	Ile	Gly 780		Leu	Glu	Asp			
5	Gln 785	Ile	Met	Ser	Leu	His 790	Ala	Glu	Ile	Met	Gly 795	Leu	Gln	Lys	Ser	Pro 800		~ ,	
3		Gly	Arg	Arg	Gln 805		Asp	Leu	Met	Glu 810		Leu	Glu	Gln	Arg 815				
	Ile	Asp	Leu	Tyr 820		Gln	Leu	Lys	His 825		Pro	Ser	Asp	His 830	Ser	Tyr			
10	Ser	Asp	Ser 835		Glu	Met	Val	Lys 840		Ile	Val	His	Thr 845		Gln	Ser			
	Gln	Asp 850		Val	Leu	Lys	Glu 855		Phe	Gly	His	Leu 860		Lys	Leu	Leu			
15	Gly 865		Lys	Gln	Lys	Ile 870	Ile	Asp	Leu	Leu	Pro 875	Lys	Val	Glu	Val	Ala 880			
		Ser	Asn	Ile	Lys 885		Ala	Asp	Asn	Thr 890		Met	Phe	Met	Gln 895	Gly			
	Lys	Arg	Gln	Lys 900		Ile	Trp	His	Leu 905		Lys	Ile	Ala	Cys 910	Thr	Gln			-
20	Ser	Ser	Ala 915		Ser	Leu	Val	Gly 920		Ser	Leu	Glu	Gly 925	Ala	Val	Thr			•
	Pro	Gln 930		Ser	Ala	Trp	Leu 935	Pro	Pro	Thr	Ser	Ala 940	Glu	His	Asp	His			
25	Ser 945	Leu	Ser	Cys	Val	Val 950	Thr	Pro	Gln	Asp	Gly 955	Glu	Thr	Ser	Ala	Gln 960		آغاره	
25		Ile	Glu	Glu	Asn 965		Asn	Cys	Leu	Gly 970		Leu	Ser	Thr	Ile 975				
	His	Glu	Ala			Glu	Gln	Gly			Met	Met	Asn		Asp	Trp		•	
30	Ser	Trp	Leu 995	980 Thr	Glu				985					990				* **	
				) INI	FORM	ו חדיד ב	v FOI	S SEC	חד כ	NO :	122:								
25										1101									
35		( :	(A)	LENG	GTH:	299	l bas	se pa									•		•
			(C)	TYPI STRA	ANDEI	ONES	S: s:	ingl	<b>e</b>										
40			(D)	TOP	OLOG:	Y: 1:	inea	c											
				MOLE FEAT		TYPI	E: cl	AMC											
45				IAN (					eque	nce									
45				) LOO ) OTI															
		(:	xi) s	SEQUI	ENCE	DES	CRIP	rion	: SE	Q ID	ио:	122:							
50															TGG Trp			48	
	1	Giu	Arg	PIO	5	Gly	пец	Arg	FIO	10	Ala	Gry	Cly	110	15	Q1u	ż		
55															CTG Leu			96	. 4
	.100	A. Y	Jiu	20	~~u	Jry	*111	-	25		J+ y		, 41	30		-1-			000
18.																			233

5	CAT His									144
3	CTA Leu 50									192
10	AAG Lys									240
15	GAA Glu									288
20	TGT Cys									336
25	TGT Cys									384
	TCT Ser 130									432
30	AAA Lys									480
35	AAA Lys									528
40	TGT Cys									576
45	GAG Glu									624
	ATG Met 210				-	-	-	 		672
50	CAG Gln									720
55	ATA Ile									768

His Leu Pro Gln Pro Asn Ser Leu Cys Ser Leu Ile Val Glu Pro Met  260 265 270 5	•
GAA AAC TGG CTA CAG TTG ATG TTG AAT TGG GAC CCT CAG CAG AGA GGA Glu Asn Trp Leu Gln Leu Met Leu Asn Trp Asp Pro Gln Gln Arg Gly 275 280 285	864
GGA CCT GTT GAC CTT ACT TTG AAG CAG CCA AGA TGT TTT GTA TTA ATG Gly Pro Val Asp Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met 290 295 300	912
GAT CAC ATT TTG AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT  Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser  305 310 315 320	960
GCA AAG ATA ATT TCT TTT CTG TTA CCA CCT GAT GAA AGT CTT CAT TCA Ala Lys Ile Ile Ser Phe Leu Leu Pro Pro Asp Glu Ser Leu His Ser 325 330 335	1008
CTA CAG TCT CGT ATT GAG CGT GAA ACT GGA ATA AAT ACT GGT TCT CAA Leu Gln Ser Arg Ile Glu Arg Glu Thr Gly Ile Asn Thr Gly Ser Gln 340 345 350	1056
GAA CTT CTT TCA GAG ACA GGA ATT TCT CTG GAT CCT CGG AAA CCA GCC Glu Leu Leu Ser Glu Thr Gly Ile Ser Leu Asp Pro Arg Lys Pro Ala 355 360 365	1104
30 TCT CAA TGT GTT CTA GAT GGA GTT AGA GGC TGT GAT AGC TAT ATG GTT Ser Gln Cys Val Leu Asp Gly Val Arg Gly Cys Asp Ser Tyr Met Val 370 375 380	1152
TAT TTG TTT GAT AAA AGT AAA ACT GTA TAT GAA GGG CCA TTT GCT TCC  Tyr Leu Phe Asp Lys Ser Lys Thr Val Tyr Glu Gly Pro Phe Ala Ser  385 390 395 400	1200
AGA AGT TTA TCT GAT TGT GTA AAT TAT ATT GTA CAG GAC AGC AAA ATA Arg Ser Leu Ser Asp Cys Val Asn Tyr Ile Val Gln Asp Ser Lys Ile 40 405 410 415	1248
CAG CTT CCA ATT ATA CAG CTG CGT AAA GTG TGG GCT GAA GCA GTG CAC Gln Leu Pro Ile Ile Gln Leu Arg Lys Val Trp Ala Glu Ala Val His 420 425 430 45	1296
TAT GTG TCT GGA CTA AAA GAA GAC TAT AGC AGG CTC TTT CAG GGA CAA Tyr Val Ser Gly Leu Lys Glu Asp Tyr Ser Arg Leu Phe Gln Gly Gln 435 440 445	1344
AGG GCA GCA ATG TTA AGT CTT CTT AGA TAT AAT GCT AAC TTA ACA AAA Arg Ala Ala Met Leu Ser Leu Leu Arg Tyr Asn Ala Asn Leu Thr Lys 450 455 460	1392
ATG AAG AAC ACT TTG ATC TCA GCA TCA CAA CAA CTG AAA GCT AAA TTG  Met Lys Asn Thr Leu Ile Ser Ala Ser Gln Gln Leu Lys Ala Lys Leu  465 470 475 480	1440 235

5	TTT Phe								1488
J	ATG Met								1536
10	ATG Met								1584
15	CTG Leu 530								1632
20	AAG Lys								1680
25	CAG Gln								1728
	CAC His								1776
30	GTG Val								1824
35	AAG Lys 610								1872
40	GAA Glu								1920
45	ATG Met								1968
	TGT Cys								2016
50	GCA Ala								2064
55	CAT His 690			_					2112

5	TCA Ser									2160
Ü	ACT Thr									2208
10	CTT Leu									2256
15	CCG Pro									2304
20	 GTG Val 770	-								2352
25	AGC Ser									2400
	CTG Leu									2448
30	CTC Leu									2496
35	GAC Asp									2544
40	TAC Tyr 850									2592
45	ACC Thr									. 2640
	GAG Glu									2688
50	AAG Lys								_	2736
55	AAG Lys							Arg		2784

5		_		GGC Gly													2832
				GAC Asp													2880
10				GCC Ala													2928
15	-			GAG Glu 980													2976
20		CTG Leu		AAG Lys	TAA												2991
			(2)	INE	FORM	OITA	1 FOE	R SE	O ID	NO:	123:						
25		<b>()</b>	(A) (B) (C)	EQUEN LENC TYPE STRA	ETH: E: ar ANDEI	996 mino ONES	amin acio 3: si	no ao i ingle	cids								
30		7)	li) N 7) FF	MOLE C	CULE ENT	TYPI TYPE	E: pi	rote: cerna	al		NO.						
35				SEQUE										_	_	<b>~</b> 3	
	1		-	Pro	5	-				10		_	-		15		
				Arg 20		_		_	25					30			
40			35	Glu				40					45				
	Glu	Leu 50	Ser	Thr	Lys	Asn	Arg 55	Glu	Arg	Trp	Cys	His 60	Glu	Ile	Gln	Ile	
45	Met 65	Lys	Lys	Leu	Asn	His 70	Ala	Asn	Val	Val	Lys 75	Ala	Cys	Asp	Val	Pro 80	
	Glu	Glu	Leu	Asn	Ile 85	Leu	Ile	His	Asp	Val 90	Pro	Leu	Leu	Ala	Met 95	Glu	
	Tyr	Cys	Ser	Gly 100	Gly	Asp	Leu	Arg	Lys 105	Leu	Leu	Asn	Lys	Pro 110	Glu	Asn	
50	Cys	Cys	Gly 115	Leu	Lys	Glu	Ser	Gln 120	Ile	Leu	Ser	Leu	Leu 125	Ser	Asp	Ile	
	Gly	Ser 130		Ile	Arg	Tyr	Leu 135		Glu	Asn	Lys	Ile 140	Ile	His	Arg	Asp	
		Lys	Pro	Glu	Asn			Leu	Gln	Asp			Gly	Lys	Ile		
55	145 His	Lvs	Ile	Ile	Asp	150 Leu		Tyr	Ala	Lvs	155 Asp		Asp	Gln	Glv	160 Ser	
		-, <b>-</b>					1	- 1 <b>-</b>		1-	2		P		1		004

					165					170					175	
	Leu	Cys	Thr	Ser	Phe	Val	Gly	Thr	Leu	Gln	Tyr	Leu	Ala	Pro	Glu	Leu
		-		180					185		_			190		
	Phe	Glu	Asn	Lvs	Pro	Tyr	Thr	Ala	Thr	Val	Asp	Tyr	Trp	Ser	Phe	Gly
5			195	•		•		200			-	-	205			•
•	Thr	Met		Phe	Glu	Cvs	Ile		Glv	Tvr	Ara	Pro		Leu	His	His
	****	210				-,-	215			- 1 -	5	220			•	
	7 011	Gln	Dro	Dhe	Thr	Trn		Glu	Lve	Tla	Live		Luc	Acn	Dro	Lvs
	225	GIII	PIO	FIIC	1111	230	III	Giu	пуз	116	235	цуз	БУЗ	тэр	rio	240
10		<b>-1</b> -	Dha	חות	C		<b>C</b> 3	Mot	C - 35	<i>α</i> 1	_	17-1	7	Dho	cor	
10	Cys	Ile	Pne	Ala		GIU	Giu	Mec	Ser		GIU	vai	Arg	PHE		SEL
		_		<b>~</b> 1	245		0			250	<b>.</b>	T 3 -	**- 3	<b>a</b> 1	255	Ma. =
	HIS	Leu	Pro		Pro	ASN	ser	Leu	-	ser	Leu	Tie	vaı		PLO	Mec
		_	_	260		_		_	265	_	_	_		270	•	<b>a</b> 1
	Glu	Asn		Leu	GIn	Leu	Met		Asn	Trp	Asp	Pro		GIn	Arg	GIY
15			275					280					285			
	Gly	Pro	Val	Asp	Leu	Thr	Leu	Lys	Gln	Pro	Arg	Cys	Phe	Val	Leu	Met
		290					295					300				
	Asp	His	Ile	Leu	Asn	Leu	Lys	Ile	Val	His	Ile	Leu	Asn	Met	Thr	Ser
	305					310					315					320
20	Ala	Lys	Ile	Ile	Ser	Phe	Leu	Leu	Pro	Pro	Asp	Glu	Ser	Leu	His	Ser
		-			325					330					335	
	Leu	Gln	Ser	Arq	Ile	Glu	Arg	Glu	Thr	Gly	Ile	Asn	Thr	Gly	Ser	Gln
				340					345	-				350		
	Glu	Leu	Leu		Glu	Thr	Glv	Ile		Leu	Asp	Pro	Ara		Pro	Ala
25			355				1	360			E		365	-		
20	Ser	Gln		Val	T.eu	Δen	Glv		Ara	Glv	Cvs	Δsn		Tyr	Met	Val
	561	370	Cys	V CL 1	LCu	1.05	375		*** 9		CyS	380	501	- /		
	Tite	Leu	Dhe	λαν	Lare	Sar		Thr	Val	Tir	Glu		Pro	Dhe	Δla	Ser
	_	Leu	FIIC	Asp	цуз	390	цуз	1111	vai	TYL	395	Gry	FIO	FIIC	AΙα	400
20	385		<b>.</b>	0	7		17- 1	N	<b>77</b>	T1-		<b>a</b> 1-	A	C 0 75	T 140	
30	Arg	Ser	Leu	ser	_	Cys	vai	ASII	IYI		Val	GIII	ASP	ser	415	116
		_	_		405	~1	<b>-</b>		_	410	_		<b>a</b> 3	71-		TT
	GIn	Leu	Pro		TIE	GIN	Leu	Arg		Val	Trp	Ата	GIU		vaı	HIS
			_	420	_	_			425	_	_	_	_,	430	<b>a</b> 1	<b>a</b> 1-
	Tyr	Val		GIA	Leu	Lys	Glu		Tyr	Ser	Arg	Leu		GIn	GIY	GIn
35			435					440				_	445			_
	Arg	Ala	Ala	Met	Leu	Ser		Leu	Arg	Tyr	Asn		Asn	Leu	Thr	Lys
		450					455					460		_		
	Met	Lys	Asn	Thr	Leu	Ile	Ser	Ala	Ser	Gln	Gln	Leu	Lys	Ala	Lys	Leu
	465					470					475					480
40	Glu	Phe	Phe	His	Lys	Ser	Ile	Gln	Leu	Asp	Leu	Glu	Arg	Tyr	Ser	Glu
					485					490					495	
	Gln	Met	Thr	Tyr	Gly	Ile	Ser	Ser	Glu	Lys	Met	Leu	Lys	Ala	Trp	Lys
				500					505					510		
	Glu	Met	Glu	Glu	Lys	Ala	Ile	His	Tyr	Ala	Glu	Val	Gly	Val	Ile	Gly
45			515		_			520	-				525			
	Tvr	Leu	Glu	asp	Gln	Ile	Met	Ser	Leu	His	Ala	Glu	Ile	Met	Gly	Leu
	- 1 -	530		•			535					540			-	
	Gln	Lys	Ser	Pro	Tvr	Glv		Ara	Gln	Glv	Asp		Met	Glu	Ser	Leu
	545	-,-			- , -	550	5	5		,	555			-,		560
50		Gln	Ara	Δla	Tle		T.e.u	Tur	Lve	Gln		Lvs	ніс	Ara	Pro	
50	GIU	GIII	213	714	565	nsp	Leu	- y -	шуз	570	<u> </u>	Ly S		9	575	
	∧ ~~	His	e-~	т~		7 ~~	C^~	<b>Th~</b>	G1		V-1	Lare	T16	Tle		ніе
	мэр	птз	ಾರ್		SCT	wah	261	TIIL		ויוכנ	vaı	пλя	116	590	Val	
	mr	17-7	a1	580	C1-	λ	λ·	17- 1	585	T	<b>~1</b>	T 0	Dh.		ui-	T.e.i
<i></i>	ınr	Val		ser	GIU	Asp	Arg		ьeu	ьys	GIU	neu		GTÀ	urz	пси
55	_	_	595	<b>.</b>	a.	~		600	_		~ 1	•	605		D	T
	Ser	Lys	Leu	Leu	GLY	Cys	Lys	Gln	Lys	Ile	lle	Asp	Leu	Leu	Pro	гла

		610					615					620				
	Val 625	Glu	Val	Ala	Leu	Ser 630	Asn	Ile	Lys	Glu	Ala 635	Asp	Asn	Thr	Val	Met 640
5	Phe	Met	Gln	Gly	Lys 645	Arg	Gln	Lys	Glu	Ile 650	Trp	His	Leu	Leu	Lys 655	Ile
		Cys		660				_	665					670		
	Gly	Ala	Val 675	Thr	Pro	Gln	Thr	Ser 680	Ala	Trp	Leu	Pro	Pro 685	Thr	Ser	Ala
10		His 690	_				695	_				700				
	705	Ser				710					715	_		_		720
15		Thr			725					730					735	
		Leu	_	740					745					750		
		Pro	755					760					765			
20		Val 770					775					780				
	785	Ser				790					795					800
25		Leu	_		805	_			_	810					815	
		Leu		820					825			_		830		
00		Asp -	835					840					845			
30	_	Tyr 850					855					860				
	865	Thr				870					875					880
35		Glu			885					890					895	
		Lys		900					905					910		
40		Lys Glu	915					920					925			
40		930					935					940				
	945	Ile				950					955					960
45		Gln			965		_	_		970		_			975	
		Leu		980	рпе	vai	ınr	ATA	985	стХ	тте	ınr	ьeu	990	nec	ASP
50	GIU	Leu	Tyr 995	гàг												
50																

## (2) INFORMATION FOR SEQ ID NO:124:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1908 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single

(D)	TOPOLOGY:	linear

- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:

5

- (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...1905
- (D) OTHER INFORMATION:

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

4.5					GGC Gly 5												48
15					GGC Gly												96
20					GAT Asp												144
25					AAG Lys												192
30					GTG Val												240
35					TTC Phe 85											_	288.
					TTC Phe												336
40					GGC Gly												384
45					GAG Glu												432
50					CAC His												480
55					AAC Asn 165												528
	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	CCC	ATC	GGC	GAC	GGC	576

	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly	
5		GTG Val															624
10		AAA Lys 210															672
45		ACC Thr															720
15		CTC Leu															768
20		GAG Glu															816
25		GGC Gly															864
30		CGC Arg 290														_	912
0.5		GGC Gly															960
35		GTC Val															1008
40		CGC Arg															1056
45		GCG Ala															1104
50		GGA Gly 370															1152
<b>6 6</b>		AAC Asn															1200
55	ccc	GGC	CCG	TCG	GAG	CAC	ATA	GAG	CGC	CGG	GTC	TCC	AAT	GCA	GGA	GGC	1248

	Pro	Gly	Pro	Ser	Glu 405	His	Ile	Glu		Arg 410	Val	Ser	Asn	Ala	Gly 415	Gly	
5														GGA Gly 430			1296
10														TCG Ser			1344
15														GCA Ala			1392
10														GCC Ala			1440
20														AGC Ser			1488
25														AGT Ser 510			1536
30														CTG Leu			1584
35			Lys											GAT Asp	_		1632
														AGT Ser			1680
40														AGG Arg			1728
45														ACG Thr 590			1776
50														CTT Leu		GAA Glu	1824
55														ATT Ile			1872
	TTC	GTC	CAG	GAG	CTG	AGG	AAG	CGG	GGT	TCT	CCC	TGA					1908 <b>243</b>

244

Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro 625 630 635

- 5 (2) INFORMATION FOR SEQ ID NO:125:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 635 amino acids
    - (B) TYPE: amino acid
    - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
  - (ii) MOLECULE TYPE: protein
  - (v) FRAGMENT TYPE: internal

15

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 30 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 220 45 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ser Glu Thr Val Ile Met 250 50 Ser Glu Thr Val Ile Cys Ser Ser Arg Ala Thr Val Met Leu Tyr Asp 265 Asp Gly Asn Lys Arg Trp Leu Pro Ala Gly Thr Gly Pro Gln Ala Phe 280 Ser Arg Val Gln Ile Tyr His Asn Pro Thr Ala Asn Ser Phe Arg Val 295 55 Val Gly Arg Lys Met Gln Pro Asp Gln Gln Val Val Ile Asn Cys Ala

245

	305					310					315					320
	Ile	Val	Arg	Gly	Val 325	Lys	Tyr	Asn	Gln	Ala 330	Thr	Pro	Asn	Phe	His 335	Gln
5	Trp	Arg	Asp	Ala 340	Arg	Gln	Val	Trp	Gly 345	Leu	Asn	Phe	Gly	Ser 350	Lys	Glu
	Asp	Ala	Ala 355	Gln	Phe	Ala	Ala	Gly 360	Met	Ala	Ser	Ala	Leu 365	Glu	Ala	Leu
		370	_	_			375		Pro			380				•
10	385		_			390			Val		395					400
•		_			405				Arg	410					415	
15				420					Pro 425					430		
			435	_				440	Pro	_			445			
		450				-	455	_	Gly			460				
20	465					470		-	Gly	_	475		_			480
					485				Lys	490					495	
25				500	_	_			Ala 505		-			510		
		_	515	_	_			520	Glu				525			
	_	530	_				535	_	Glu	_		540				
30	545					550			Arg		555					560
		_	_		565		-		Ser	570					575	
35				580					Glu 585					590		
			595					600					605			Glu
40		610	_	_			615	_	Val	-		620	lle	IIe	GIU	Ala
40	Pne 625	Val	GIn	Glu	Leu	Arg 630	Lys	Arg	Gly	ser	635					
			(2	) INI	FORM	ATIO	v FO	R SE	Q ID	NO:	126:					
45		(				CHAR 132										
			(B)	TYP	E: n	ucle: DNES:	ic a	cid								
50						Y: 1:			<del>u</del>							
50			ii) ix)			TYP	E: c	DNA								
			,		<b>-</b> ·							-				

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...1326(D) OTHER INFORMATION:

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

		`-	, -							-							
5		GTG Val															48
10		GAG Glu															96
15		GGC Gly															144
10		ACC Thr 50															192
20		ACC Thr															240
<b>2</b> 5		CAC His															288
30		ACC Thr															336
35		AAG Lys															384
33		GAC Asp 130														TAC Tyr	432
40		TAC Tyr															480
45		ATC Ile													_		528
50		CAG Gln															576
55		GTG Val							Tyr								624
55	AGC	AAA	GAC	CCC	AAC	GAG	AAG	CGC	GAT	CAC	ATG	GTC	CTG	CTG	GAG	TTC	672

	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe		
5											GAC Asp 235						· 720	
10											GCT Ala						768	
15											AAG Lys						816	
13											TAT Tyr						864	
20											GGA Gly						912	
25											TAT Tyr 315						960	
30											ATG Met						1008	
25											AAG Lys						1056	
35											CTG Leu						1104	
40											GAG Glu						1152	
45											GAT Asp 395						1200	
50											AAG Lys				_	_	1248	
			-								GCT Ala						1296	
55	GGG	AAG	AAA	AAA	TCT	GGT	TGC	CTT	GTC	TTG	TGA						132	9 <b>247</b>

248

Gly Lys Lys Ser Gly Cys Leu Val Leu 435 440

- 5 (2) INFORMATION FOR SEQ ID NO:127:
  - (i) SEQUENCE CHARACTERISTICS:
    - (A) LENGTH: 442 amino acids
    - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
    - (D) TOPOLOGY: linear
    - (ii) MOLECULE TYPE: protein
    - (v) FRAGMENT TYPE: internal

15

10

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:
- Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ala Ala Ile Arg Lys Lys 245 250 50 Leu Val Ile Val Gly Asp Gly Ala Cys Gly Lys Thr Cys Leu Leu Ile 265 Val Phe Ser Lys Asp Gln Phe Pro Glu Val Tyr Val Pro Thr Val Phe 280 Glu Asn Tyr Val Ala Asp Ile Glu Val Asp Gly Lys Gln Val Glu Leu 55

Ala Leu Trp Asp Thr Ala Gly Gln Glu Asp Tyr Asp Arg Leu Arg Pro

-21-

	305					310					315					320		
		Ser			325					330					335			
5	Ser	Pro	Asp	Ser 340	Leu	Glu	Asn	Ile	Pro 345	Glu	ГÀЗ	Trp	Thr	Pro 350	Glu	Val		
	Lys	His	Phe 355	Cys	Pro	Asn	Val	Pro 360	Ile	Ile	Leu	Val	Gly 365	Asn	Lys	Lys		
	Asp	Leu 370	Arg	Asn	Asp	Glu	His	Thr	Arg	Arg	Glu	Leu 380	Ala	Lys	Met	Lys		
10	Gln 385	Glu	Pro	Val	Lys	Pro 390		Glu	Gly	Arg	Asp 395		Ala	Asn	Arg	Ile 400		
		Ala	Phe	Gly			Glu	Cys	Ser			Thr	Lys	Asp				
	Arg	Glu	Val		405 Glu	Met	Ala	Thr		410 Ala	Ala	Leu	Gln		415 Arg	Arg		
15	Gly	Lys	Lys	420 Lys	Ser	Gly	Cys	Leu	425 Val	Leu				430				
			435					440										
20			(2)	INE	FORMA	OITA	1 FOF	R SEC	Q ID	NO: 1	28:							
		( j	i) SI	EQUEN LENC														
			(B)	TYPE	E: nı	ıclei	ic ad	cid										
25				STRA				_	2								•	
		( :	ii) N	MOLE	CULE	TYPE	E: cI	ANC										
		( i	ix) I	FEAT	JRE:													
30				NAM LOC				-	eque	ıce							:	
				OTI														
35		()	ci) S	SEQUI	ENCE	DESC	CRIPT	rion	: SE	Q ID	NO: 1	128:						
33		GAC															48	
	Met 1	Asp	His	Tyr	Asp 5	ser	GIN	GIN	Thr	Asn 10	Asp	Tyr	мес	GIN	15	Giu		
40		GAC															96	
	Glu	Asp	Trp	Asp 20	Arg	Asp	Leu	Leu	Leu 25	Asp	Pro	Ala	Trp	Glu 30	Lys	Gln		
	CAG	AGA	AAG	ACA	TTC	ACG	GCA	TGG	TGT	AAC	TCC	CAC	CTC	CGG	AAG	GCG	144	
45		Arg														_		
	000	202		3 m/a	an a	7 7 C	A TO C		C N C	an a	mmc.	ccc		ccc	CTT.CT	አ አ C	192	
		ACA Thr					Ile					Arg					132	
50		50					55					60				~		
		ATG Met															240	
55	65				÷	70					75					80		;
	GAG	CGA	GGC	AAG	ATG	AGA	GTG	CAC	AAG	ATC	TCC	AAC	GTC	AAC	AAG	GCC	288	
																		249

										200								
	Glu	Arg	Gly	Lys	Met 85	Arg	Val	His	Lys	Ile 90	Ser	Asn	Val	Asn	Lys 95	Ala		
_		GAT															336	
5	Leu	Asp	Phe	Ile 100	Ala	Ser	Lys	Gly	Val 105	Lys	Leu	Val	Ser	Ile 110	Gly	Ala		
		GAA Glu															384	
10			115		•	•		120	•		_		125					
	ACC	ATC	ATC	CTG	CGC	AGG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	432	
	Thr	Ile 130	Ile	Leu	Arg	Arg	-	Pro	Pro	Val	Ala		Met	Val	Ser	Lys		
15							135					140						
		GAG Glu															480	
	145	0.10	Olu	Lea	1110	150	Cly	var	Val	110	155	Deu	Vai	Giu	Deu	160		
20	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	GAG	GGC	528	
		Asp			Gly					Val					Glu			
					165					170					175			
25		GCC															576	
20	ASP	Ala	1111	180	GIY	гур	Leu	1111	185	гÀг	Pne	iie	Cys	190	THE	GIY		
	AAG	CTG	CCC	GTG	רככ	TGG	רככ	ACC	CTC	CTC	ACC	ልሮሮ	CTG	ACC	TAC	GGC	624	
		Leu	Pro														024	
30			195					200					205					
	_	CAG															672	
	vai	Gln 210	Cys	Phe	Ser	Arg	Tyr 215	Pro	Asp	His	Met	Lys 220	Gln	His	Asp	Phe		
35	ጥጥር	AAG	TOO	ccc	א ידירי	ccc	C A A	ccc		CTTC	C A C	a.a	cac	7 CC	3 TO C	mmc	720	
		Lys															720	
	225					230					235					240		
40		AAG															768	
	Phe	Lys	Asp	Asp	Gly 245	Asn	Tyr	Lys	Thr	Arg 250	Ala	Glu	Val	Lys	Phe 255	Glu		
	999	G2 G	200	ama			~~~											
45		GAC Asp															816	
				260					265					270				
		GAC															864	
50	Glu	Asp	Gly 275	Asn	Ile	Leu	Gly	His 280	Lys	Leu	Glu	Tyr	Asn 285	Tyr	Asn	Ser		
	~																	
		AAC Asn															912	
55		290		-			295	Ŀ	4 -		<u>.</u> -	300	- <b>.</b>		<b>3</b> -			
55	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC	AGC	GTG	CAG	CTC	GCC	960	
																		250

PCT/DK98/00145 .

										251							
	Asn 305	Phe	Lys	Ile	Arg	His 310	Asn	Ile	Glu	Asp	Gly 315	Ser	Val	Gln	Leu	Ala 320	
5		CAC His															1008
10		GAC Asp															1056
15		GAG Glu															1104
13		ATC Ile 370										TAA					1140
20			(2)	INI	FORMA	OITA	4 FOI	R SEC	Q ID	NO : 3	129:						
25		( :	(A) (B) (C)	LENG TYPI STRA	NCE ( GTH: E: an ANDEI OLOG!	379 mino ONES	amin acio 3: s:	no ad i ingle	cids								
30					CULE		_										•
		()	ci) s	EQUI	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	129:					
35	1	Asp			5					10					15		*
		Asp Arg		20					25					30			
40		Thr	35					40	_				45				
	Leu	50 Met	Leu	Leu	Leu	Glu	55 Val	Ile	Ser	Gly	Glu	60 Arg	Leu	Ala	Lys		
45	65 Glu	Arg	Gly	Lys	Met 85	70 Arg	Val	His	Lys	Ile 90	75 Ser	Asn	Val	Asn	Lys 95	80 Ala	
40	Leu	Asp	Phe	Ile 100		Ser	Lys	Gly	Val 105		Leu	Val	Ser	Ile 110		Ala	
	Glu	Glu	Ile 115		Asp	Gly	Asn	Val 120		Met	Thr	Leu	Gly 125	Met	Ile	Trp	
50	Thr	Ile 130	Ile	Leu	Arg	Arg	Asp 135	Pro	Pro	Val	Ala	Thr 140	Met	Val	Ser	Lys	
	Gly 145	Glu	Glu	Leu	Phe	Thr 150	Gly	Val	Val	Pro	Ile 155	Leu	Val	Glu	Leu	Asp 160	
55			Val	Asn	Gly 165		Lys	Phe	Ser	Val 170		Gly	Glu	Gly	Glu 175	Gly	
	Asp	Ala	Thr	Tyr		Lys	Leu	Thr	Leu		Phe	Ile	Cys	Thr		Gly	

				100					103					190				
	Lys	Leu	Pro 195	Val	Pro	Trp	Pro	Thr 200	Leu	Val	Thr	Thr	Leu 205	Thr	Tyr	Gly		
5	Val	Gln 210	Cys	Phe	Ser	Arg	Tyr 215	Pro	Asp	His	Met	Lys 220	Gln	His	Asp	Phe		
		Lys	Ser	Ala	Met		Glu	Gly	Tyr	Val		Glu	Arg	Thr	Ile			
	225 Dho	Lys	7 ~~	N.a.m	C1	230	T1	T	Th~	N ~~	235	C1.,	V-1	T v/C	Dhe	240		
	Pne	гуя	Asp	Asp	245	ASII	ıyı	гуѕ	1111	250	Ala	GIU	vai	пуз	255	Giù		
10	Gly	Asp	Thr	Leu 260	Val	Asn	Arg	Ile	Glu 265		Lys	Gly	Ile	Asp 270	Phe	Lys		
	Glu	Asp	Gly 275	Asn	Ile	Leu	Gly	His 280	Lys	Leu	Glu	Tyr	Asn 285	Tyr	Asn	Ser		
15	His	Asn 290	Val	Tyr	Ile	Met	Ala 295	Asp	Lys	Gln	Lys	Asn 300	Gly	Ile	Lys	Val		
	Asn 305	Phe	Lys	Ile	Arg	His 310	Asn	Ile	Glu	Asp	Gly 315	Ser	Val	Gln	Leu	Ala 320		
	Asp	His	Tyr	Gln	Gln 325	Asn	Thr	Pro	Ile	Gly 330	Asp	Gly	Pro	Val	Leu 335	Leu		
20	Pro	Asp	Asn			Leu	Ser	Thr		Ser	Ala	Leu	Ser		Asp	Pro		
	λαη	Glu	Lve	340	λαρ	uic	Met	Val	345	Len	Glu	Dhe	Val	350	Δla	Δla		
	ASII	GIU	цуs 355	Arg	Asp	птэ	Mec	360	пеп	пеп	GIU	FIIC	365	1111	VIG	ALG		
	Gly	Ile	Thr	Leu	Gly	Met		Glu	Leu	Tyr	Lys							
25		370					375											
			(2)	INE	FORM	OITA	1 FOF	R SEC	Q ID	NO: 3	L30:							
		(i	.) SE	OUE	ICE (	CHARA	ACTE	RIST	ICS:									
30		, –	(A)	LENC	GTH:	3516	bas	se pa										
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35				EATU		TYPE	s: CI	JNA										
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40						ON: I												
			(2)	011		0.												
		()	ci) S	EQUI	ENCE	DESC	CRIP	rion	: SE	Q ID	NO:	130:						
		GTG															48	
45	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu		
	-				J					10								
		GAG Glu															96	
50	Val	GIU	Leu	20	GIÀ	Asp	vai	ASII	25	HIS	пуѕ	PHE	Ser	30	SEL	Gly		
	<b>a</b>	000	ar c	000	~~~	000	200	m	000	n * ~	CIEC .	7.00	ama	7 7 C	than Ca	እጥር	744	
		GGC Gly															144	
		- 1	35	- 1	- 2			40	- <b>-</b> I	_1 -2			45	1 -				
55	TCC	700	200	000	7 7 C	CTC.	000	or-	~~~	maa.	000	7.00	CTC	CTC	7.00	አ <i>ርር</i>	192	
	TGC	ACC	ACC	GGC	AAG	CIG	CCC	GTG	CCC	TGG	CCC	ACC	CIC	G I G	ACC	ACC	132	252

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
5					GTG Val												240
10					TTC Phe 85												288
15					TTC Phe										Ala	_	336
13					GGC Gly												384
20					GAG Glu												432
25					CAC His												480
30					AAC Asn 165												528
25					GAC Asp												576
35					CCC Pro										_		624
40					AAC Asn												672
45					GGG Gly												720
50					CGA Arg 245												768
E.F.					GCC Ala											-	816
55	GAG	CTT	GAC	TTC	TCC	ATC	CTC	TTC	GAC	TAT	GAG	TAT	TTG	AAT	CCG	AAC	864

	Glu	Leu	Asp 275	Phe	Ser	Ile	Leu	Phe 280	Asp	Tyr	Glu	Tyr	Leu 285	Asn	Pro	Asn	
5		GAA Glu 290															912
10		TAC Tyr															960
15		GCT Ala															1008
		GTA Val															1056
20		GGC Gly															1104
25		GCA Ala 370															1152
30		CCT Pro															1200
35		CCC Pro															1248
33		AGC Ser											•				1296
40		TCG Ser															1344
45		CAG Gln 450															1392
50		ATG Met															1440
55		TCG Ser															1488
JJ	AAG	CGG	AGG	CAT	TCG	TGC	GCC	GAG	GCC	TTG	GTT	GCC	CTG	CCG	CCC	GGA	1536

										200								
	Lys	Arg	Arg	His 500	Ser	Cys	Ala	Glu	Ala 505	Leu	Val	Ala	Leu	Pro 510	Pro	Gly		
5					CGC Arg												1584	٠.
10					GAC Asp												1632	
15					ATC Ile												1680	
13					CCC Pro 565												1728	
20					GCC Ala												1776	
25					TTC Phe												1824	
30					TCC Ser												1872	
0.5					ATT Ile												1920	
35					TGG Trp 645												1968	
40					CAG Gln												2016	
45					GGG Gly												2064	
50					GGC Gly										_	_	2112	
					GCT Ala												2160	
55	CAG	GTG	CAC	CGA	ATC	ACG	GGG	AAA	ACT	GTC	ACC	ACC	ACC	AGC	TAT	GAG	2208	255

										200							
	Gln	Val	His	Arg	Ile 725	Thr	Gly	ГÀЗ	Thr	Val 730	Thr	Thr	Thr	Ser	Tyr 735	Glu	
5		ATA Ile															2256
10		AAC Asn															2304
45		GCC Ala 770															2352
15		ACG Thr															2400
20		AGA Arg															2448
25		CGA Arg															2496
30		TGC Cys															2544
25		ACA Thr 850														_	2592
35		CAA Gln															2640
40		AAC Asn															2688
45		ACA Thr															2736
50		AGT Ser															2784
		GAG Glu 930											Cys				2832
55	CAT	GGA	GGC	CTG	GGG	AGC	CAG	CCT	TAC	TAC	ccc	CAG	CAC	CCG	ATG	GTG	2880

257

	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960	
5			TCC Ser														2928
10			ACG Thr														2976
45			GCC Ala 995				Gln					Leu					3024
15	Leu		TAT Tyr			Pro					Ala						3072
20			CAC His		Ser					Ala					Gln		3120
25			CTG Leu	Leu					Thr					Ser			3168
30			TAC Tyr					Gln					Gly				3216
		Phe	CAG Gln 1075				Tyr					Ala					3264
35	Arg		GGC Gly	_		Pro					Gln						3312
40			CCC Pro		Val					Asn					Arg	_	3360
45			AAC Asn	Gly					Asp					Leu			3408
50			ACC Thr					Gln					Thr				3456
		Val	AAT Asn 1155	Glu			Arg					Gly					3504
	ТАА	CAG	ACG	TAA							٠						∵3516 <b>257</b>

 $(\mathbf{x}_{i})_{i=1}^{n}, \ldots, (\mathbf{x}_{i})_{i=1}^{n}, \ldots, (\mathbf{x}_{i})_{i=1}^{n$ 

258

Asn Gln Thr 1170

5 (2) INFORMATION FOR SEQ ID NO:131: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1171 amino acids (B) TYPE: amino acid 10 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 40 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 55 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 30 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 35 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 170 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 220 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro 250 245 Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp 50 265 Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn 280

300

Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro

Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro

295

WO 98/45704 PCT/DK98/00145 .

										200						
	305					310					315					320
	Leu	Ala	Ser	Leu	Ser 325	Gly	Glu	Pro	Pro	Gly 330	Arg	Phe	Gly	Glu	Pro 335	Asp
5	Arg	Val	Gly	Pro 340	Gln	Lys	Phe	Leu	Ser 345	Ala	Ala	Lys	Pro	Ala 350	Gly	Ala
	Ser	Gly	Leu 355	Ser	Pro	Arg	Ile	Glu 360	Ile	Thr	Pro	Ser	His 365	Glu	Leu	Ile
	Gln	Ala 370	Val	Gly	Pro	Leu	Arg 375	Met	Arg	Asp	Ala	Gly 380	Leu	Leu	Val	Glu
10	Gln 385	Pro	Pro	Leu	Ala	Gly 390	Val	Ala	Ala	Ser	Pro 395	Arg	Phe	Thr	Leu	Pro 400
	Val	Pro	Gly	Phe	Glu 405	Gly	Tyr	Arg	Glu	Pro 410	Leu	Cys	Leu	Ser	Pro 415	Ala
15	Ser	Ser	Gly	Ser 420	Ser	Ala	Ser	Phe	Ile 425	Ser	Asp	Thr	Phe	Ser 430	Pro	Tyr
	Thr	Ser	Pro 435	Cys	Val	Ser	Pro	Asn 440	Asn	Gly	Gly	Pro	Asp 445	Asp	Leu	Cys
		450	Phe				455					460				
20	465		Ser			470					475					480
			Pro		485					490					495	
25	_	_	Arg	500		_			505					510		
			Pro 515		_		_	520					525			
20		530	Pro		_		535					540				
30	545		Ala			550					555					560
			Gly		565					570					575	
35			Ser Val	580					585					590		
			595 Pro					600					605			
40		610	Pro				615					620				
10	625		Leu			630					635					640
			Glu		645					650					655	
45			Ser	660					665					670		
			675 Leu					680					685			
50		690	Gly				695					700				
	705		His			710		_			715					720
	Lys	Ile	Val	Gly	725 Asn	Thr	Lys	Val		730 Glu	Ile	Pro	Leu		735 Pro	Lys
55	Asn	Asn	Met	740 Arg	Ala	Thr	Ile	Asp	745 Cys	Ala	Gly	Ile	Leu	750 Lys	Leu	Arg

260

			755					760					765			
	Asn	Ala 770	Asp	Ile	Glu	Leu	Arg 775	Lys	Gly	Glu	Thr	Asp 780	Ile	Gly	Arg	Lys
5	Asn 785	Thr	Arg	Val	Arg	Leu 790	Val	Phe	Arg	Val	His 795	Ile	Pro	Glu	Ser	Ser 800
	Gly	Arg	Ile	Val	Ser 805	Leu	Gln	Thr	Ala	Ser 810	Asn	Pro	Ile	Glu	Cys 815	Ser
		Arg		820					825			_		830		_
10		Cys	835			_	_	840					845	_		
		Thr 850					855					860				
15	865	Gln				870					875					880
		Asn			885					890	_	_			895	
		Thr		900					905					910		
20	_	Ser	915					920	-				925			_
		Glu 930					935					940	·,			
25		Gly	Gly	Leu	Gly		Gln	Pro	Tyr	Tyr		Gln	His	Pro	Met	
23	945 Ala	Glu	Ser	Dro	Ser	950 Cve	T.e.u	Val	Δl =	Thr	955 Met	Δla	Dro	Cve	Gln	960 Gln
	AIG	Q1u	501	110	965	Cys	neu	vai	AIG	970	Mec	AIG	rio	Cys	975	QIII
		Arg		980					985					990		
30		Ala	995				:	1000		_			1005			
		Gly 1010	_				1015				-	1020				
25		Ala	His	Arg			Leu	Val	His		_	Ser	Gln	Gly		
35	025 Ser	Ala	Len	Lau		1030	Cor	Dro	Th≻		1035	Cln.	Nlο	Car		1040 Vəl
	261	AIA	Deu		1045	PIO	261	PIO		1050	GIII	GIII	Ala		1055	Vai
	Ile	His	Tyr	Ser	Pro	Thr	Asn	Gln	Gln	Leu	Arg	Cys	Gly	Ser	His	Gln
				1060					1065					1070		
40	Glu	Phe	Gln 1075	His	Ile	Met		Cys 1080	Glu	Asn	Phe		Pro 1085	Gly	Thr	Thr
	Ara	Pro		Pro	Pro	Pro			Gln	Glv	Gln			Ser	Pro	Glv
		1090	<b>-</b> 1				1095	-01	0	017		1100				1
		Tyr	Pro	Thr			Gln	Gln	Gln			Thr	Ser	Gln		
45	105	<b>.</b>	<b>-</b>	~ 1		1110		_	_		1115	~ 7		_		1120
	АТА	Lys	Asn		Pro 1125	Pro	vaı	Ser	_	Gin 1130	rys	Glu	val		Pro 1135	Ala
	Gly	Val				Gln	Glu				Asp	Gln				Asp
50	Asp	Val			Ile	Ile				Phe	Ser	_			Ala	Arg
	Asn	Gln														
		1170														

55 (2) INFORMATION FOR SEQ ID NO:132:

5		i)	(B) (C)	LENG TYPE STRA TOPO	TH: I: nu NDEI LOGY CULE	3546 iclei ONESS	bas c ac s: si near	se pa id ngle	airs									
10			(B)	NAM LOC	CATIC	N: 3	13	543	equer	nce								
15		AAC	GCC	ccc	GAG	CGG	CAG	CCC	CAA	CCC		GGC Gly					48	
20												CTT Leu					96	
25												GAA Glu					144	
30	His	Lys 50	Val	Ala	Ser	Pro	Pro 55	Ser	Gly	Pro	Ala	TAC Tyr 60	Pro	Asp	Asp	Val	1,92	
35	Met 65	Asp	Tyr	Gly	Leu	Lys 70	Pro	Tyr	Ser	Pro	Leu 75	GCT Ala	Ser	Leu	Ser	Gly 80	240	
	Glu	Pro	Pro	Gly	Arg 85	Phe	Gly	Glu	Pro	Asp 90	Arg	GTA Val	Gly	Pro	Gln 95	Lys	288	
40	Phe	Leu	Ser	Ala 100	Ala	Lys	Pro	Ala	Gly 105	Ala	Ser	GGC Gly	Leu	Ser 110	Pro	Arg	336	
45	Ile	Glu	Ile 115	Thr	Pro	Ser	His	Glu 120	Leu	Ile	Gln	GCA Ala	Val 125	Gly	Pro	Leu	384	
50	Arg	Met 130	Arg	Asp	Ala	Gly	Leu 135	Leu	Val	Glu	Gln	CCT Pro 140	Pro	Leu	Ala	Gly	432	
55												CCC Pro					480	
	TAC	CGC	GAG	CCG	CTT	TGC	TTG	AGC	CCC	GCT	AGC	AGC	GGC	TCC	TCT	GCC	528	261

262

									•	202							
	Tyr	Arg	Glu	Pro	Leu 165	Cys	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala	
*	AGC	ጥጥር	<b>አ</b> ጥጥ	тст	GAC	»CC	ጥጥር	TCC	רככ	тас	ACC	TCG	CCC	TGC	GTC	TCG	576
5					Asp										_		3,0
	CCC	ААТ	AAC	GGC	GGG	CCC	GAC	GAC	CTG	TGT	CCG	CAG	TTT	CAA	AAC	ATC	624
					Gly												
10			195					200					205				
					TCC												672
	Pro		His	Tyr	Ser	Pro		Thr	Ser	Pro	Ile		Ser	Pro	Arg	Thr	
15		210					215					220					
13	AGC	CTC	GCC	GAG	GAC	AGC	ጥርር	СТС	GGC	CGC	CAC	TCG	כככ	GTG	CCC	CGT	720
					Asp												, 20
	225					230	-1		1	<b>J</b>	235					240	
20	CCG	GCC	<b>דככ</b>	CGC	TCC	тса	TCG	ССТ	сст	GCC	ΔΔα	CGG	AGG	САТ	TCG	TGC	768
20					Ser												, 00
				5	245				1	250	_1		_		255	•	
	GCC	GAG	GCC	TTG	GTT	GCC	CTG	CCG	CCC	GGA	GCC	TCA	CCC	CAG	CGC	TCC	816
25	Ala	Glu	Ala	Leu	Val	Ala	Leu	Pro	Pro	Gly	Ala	Ser	Pro		Arg	Ser	
				260					265					270			
	000	200	000	maa	CCG	a a a	000	man.	mam	an a	arc.	CCA	ccc	CAC	CAC	CAC	864
					Pro											_	804
30	Arg	261	275	Ser	PIO	GIII	PIO	280	Ser	птэ	vai	AIA	285	GIII	rsb	mis	
00			2,3					200									
	GGC	TCC	CCG	GCT	GGG	TAC	CCC	CCT	GTG	GCT	GGC	TCT	GCC	GTG	ATC	ATG	912
	Gly	Ser	Pro	Ala	Gly	Tyr	Pro	Pro	Val	Ala	Gly	Ser	Ala	Val	Ile	Met	
		290					295					300					
35																	
					AGC												960
	_	Ата	Leu	Asn	Ser		Ата	Thr	Asp	ser		Cys	GIY	ire	PIO	320	
	305					310					315					320	
40	AAG	ATG	TGG	AAG	ACC	AGC	CCT	GAC	CCC	TCG	CCG	GTG	TCT	GCC	GCC	CCA	1008
	Lys	Met	Trp	Lys	Thr	Ser	Pro	Asp	Pro	Ser	Pro	Val	Ser	Ala	Ala	Pro	
					325					330					335		
45					CTG												1056
45	ser	гÀг	Ala	_	Leu	Pro	Arg	His		Tyr	Pro	Ата	vaı	350	Pne	Leu	
				340					345					330			
	GGG	CCC	TGC	GAG	CAG	GGC	GAG	AGG	AGA	AAC	TCG	GCT	CCA	GAA	TCC	ATC	1104
	Gly	Pro	Cys	Glu	Gln	Gly	Glu	Arg	Arg	Asn	Ser	Ala	Pro	Glu	Ser	Ile	
50	-		355			-		360	_				365				
					CCC												1152
	Leu		Val	Pro	Pro	Thr	_	Pro	Lys	Pro	Leu		Pro	Ala	тте	Pro	
55		370					375					380					
	ATC	TGC	AGC	ATC	CCA	GTG	ACT	GCA	TCC	СТС	CCT	CCA	CTT	GAG	TGG	CCG	1200
								-017		-10		- <b></b>					

	Ile 385	Cys	Ser	Ile	Pro	Val 390	Thr	Ala	Ser	Leu	Pro 395	Pro	Leu	Glu	Trp	Pro 400	
5									GAG Glu								·-1248
10									GAG Glu 425								1296
15									CCT Pro								1344
15									CAG Gln								1392
20									TTC Phe								1440
25									TAT Tyr								1488
30									CCC Pro 505								1536
0.5									CTT Leu								1584 ÷
35									AGA Arg								1632
40									TCC Ser					_			1680
45									TGC Cys								1728
50									ACA Thr 585								1776
									CAG Gln								1824
55	GTT	GTG	TTT	ACT	GAG	AAG	ACC	ACA	GAT	GGA	CAG	CAA	ATT	TGG	GAG	ATG	1872

	Val	Val 610	Phe	Thr	Glu	Lys	Thr 615	Thr	Asp	Gly	Gln	Gln 620	Ile	Trp	Glu	Met	
5									AGC Ser								1920
10									CAT His								1968
									AGA Arg 665								2016
15									ATC Ile								2064
20									CCC Pro								2112
25									ATG Met								2160
30									CAG Gln								2208
35									CAG Gln 745								2256
									AGC Ser								2304
40									CTT Leu								2352
45									CAG Gln								2400
50									CCT Pro								2448
55									CAC His 825								2496
	TAC	TGC	GAG	AAT	TTC	GCA	CCA	GGC	ACC	ACC	AGA	CCT	GGC	CCG	CCC	CCG	2544

	Tyr	Cys	Glu 835	Asn	Phe	Ala	Pro	Gly 840	Thr	Thr	Arg	Pro	Gly 845	Pro	Pro	Pro			
5															GTC Val			2592	
10															CCC Pro			2640	
45															AAA Lys 895			2688	
15															ATT Ile			2736	
20															ATT Ile			2784	
25															ATG Met		**	2832	
30															GTC Val	GAG Glu 960		2880	. <u>-</u> ,
																GGC Gly		2928	
35															TGC Cys	ACC Thr	÷	2976	
40							Pro					Val			CTG Leu			3024	
45	Tyr					Phe					Asp				CAG Gln			3072	
50					Ser					Gly					CGC Arg			3120	
				Lys			-		Tyr					Glu	GTG Val			3168	
	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	GAC		3216	265

	Phe G	lu Gl	y Asp 1060	Thr	Leu	Val		Arg 1065	Ile	Glu	Leu		Gly 1070	Ile	Asp	
5			G GAC u Asp 5			Ile					Leu					3264
10	AAC A Asn S				Tyr					Lys						3312
	AAG G Lys V 1105		C TTC n Phe	Lys					Ile					Val		3360
15	CTC G Leu A		p His					Thr					Gly			3408
20	CTG C Leu L						Leu					Ala				3456
25	GAC C Asp P					Asp					Leu					3504
30			G ATC y Ile		Leu					Leu			AAT			3546
		(	2) IN	FORM	ATIOI	N FOE	R SE(	Q ID	NO:1	133:						
35		(A (B (C	SEQUE ) LEN ) TYP ) STR	GTH: E: ar ANDEI	118: mino ONES:	l ami acio S: s:	ino a d ingle	acids	5							
40		(ii)	) TOP MOLE FRAGM		TYP	rg :3	rote									
45		(xi)	SEQU	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	133:					
	Met A	sn Al	a Pro	Glu 5	Arg	Gln	Pro	Gln	Pro 10	Asp	Gly	Gly	Asp	Ala 15	Pro	
	Gly H	lis Gl	u Pro 20	Gly	Gly	Ser	Pro	Gln 25	Asp	Glu	Leu	Asp	Phe 30	Ser	Ile	
50		35			_		40					45			_	
•	5	50	l Ala			55		_			60					
55	65		r Gly		70		_			75					80	
			1	3		1				3		1			4	

										201						
					85					90					95	
	Phe	Leu	Ser	Ala 100	Ala	Lys	Pro	Ala	Gly 105	Ala	Ser	Gly	Leu	Ser 110	Pro	Arg
5	Ile	Glu	Ile 115	Thr	Pro	Ser	His	Glu 120	Leu	Ile	Gln	Ala	Val 125	Gly	Pro	Leu
		Met 130					135					140				-
	145	Ala				150					155		_			160
10		Arg			165					170			_		175	
		Phe		180					185	_				190		
15		Asn	195					200		_			205			
		Ala 210					215					220			_	
00	225	Leu				230					235					240
20		Ala		_	245				_	250	-	_	_		255	_
		Glu		260					265	_				270	_	
25		Ser	275					280					285		_	
		Ser 290					295				_	300				
30	305	Ala				310			-		315	_	_			320
30		Met			325					330					335	
		Lys Pro		340					345	_				350		
35		Leu	355					360					365			
		370 Cys					375		_			380				
40	385					390					395					400
		Pro			405			_		410	-				415	
		Lys		420				_	425			_		430		
45		Glu	435			_	_	440					445		_	_
		450 Arg					455					460	_			_
50	465	Lys				470				_	475					480
		Val			485				-	490	-			_	495	
		Asp		500					505					510		
55			515					520					525			Leu

		530					535					540				
	Val	Phe	Arg	Val	His	Ile	Pro	Glu	Ser	Ser	Gly	Arq	Ile	Val	Ser	Leu
	545		_			550					555					560
	Gln	Thr	Ala	Ser	Asn	Pro	Ile	Glu	Cvs	Ser		Ara	Ser	Ala	His	
5					565				. 2	570		5			575	
	Leu	Pro	Met	Val	Glu	Ara	Gln	Asp	Thr		Ser	Cvs	Len	Val		Glv
				580		5			585	p	501	Cyb		590	- 7 -	Cry
	Glv	Gln	Gln		Ile	Leu	Thr	Glv		Δsn	Dhe	Thr	Ser		Ser	Lve
	1		595					600	0111		1110	****	605	Olu	001	Lys
10	Val	Va 1		Thr	Glu	Lvs	Thr		Acn	Gly	Gln	Gla		Trn	Glu	Mot
	<b>V</b> 44	610	1110	****	U L U	<b>1</b> 1 y 5	615	1111	rap	Gry	GIII	620	116	тър	Giu	Mec
	Glu		Thr	Va 1	Asp	Lve		Lvc	802	Cln	Dro		Mot	Len	Dho	17.3
	625	2114		V 44 1	тър	630	АЗР	БуЗ	Ser	GIII	635	ASII	Met	цец	FILE	640
		Tle	Pro	Glu	Tyr		Δen	Luc	uic	Tla		Thr	Dro	Wa 1	Luc	
15	Gru	110	110	Giu	645	Arg	VOII	пуъ	nis	650	Arg	1111	PIO	vai	655	val
13	Λcn	Dhe	TVY	V-1	Ile	λαη	C1	Tva	λ <b>~~</b> ~		7 w	C	~1 n	Dwa		774
	ASII	FIIC	LYL	660	116	ASII	GIŞ	пуѕ		гÀг	Arg	Ser	GIII		GIII	HIS
	Dhe	Thr	Tier		Dro	V-1	Dro	7 J -	665	T	(T)	a1	Dwa	670	A	<b>a</b> 1
	FIIC	TIIL	675	птэ	Pro	vai	PIO		TIE	гаг	Int	GIU		THE	Asp	GIU
20	m	7 ~ ~		mh w	T 0	т1.	<b>~</b>	680	D	m \	***	<b>01</b>	685	<b>.</b>	<b>61</b>	
20	ıyı		PIO	1111	Leu	116		ser	Pro	Thr	HIS	-	GIA	Leu	GIY	ser
	<b>01</b> -	690	m	<b></b>	D	<b>a</b> 1	695	_				700	_	_	_	_
		Pro	Tyr	Tyr	Pro		HIS	Pro	Met	Val		Glu	Ser.	Pro	Ser	
	705			<b>~</b> 1		710	_	_			715	_			_	720
25	Leu	vai	Ala	Thr	Met	Ala	Pro	Cys	GIn		Phe	Arg	Thr	GIA		Ser
25	_	_	_		725	_				730		_			735	
	ser	Pro	Asp		Arg	Tyr	GIn	GIn		Asn	Pro	Ala	Ala		Leu	Tyr
		_	_	740	_	_	_	_	745			_		750	_	
	GIn	Arg		Lys	Ser	Leu	Ser		Ser	Leu	Leu	Gly		Gln	Gln	Pro
00	_ •	_	755			_	_	760		_		_	765			
30	Ala		Met	Ala	Ala	Pro		Ser	Leu	Ala	Asp		His	Arg	Ser	Val
	_	770	•			_	775		_			780				
		Val	His	Ala	Gly		GIn	Gly	Gln	Ser		Ala	Leu	Leu	His	
	785	_				790					795					800
	Ser	Pro	Thr	Asn	Gln	Gln	Ala	Ser	Pro		Ile	His	Tyr	Ser	Pro	Thr
35		_	_		805					810					815	
	Asn	Gln	Gln		Arg	Cys	Gly	Ser	His	Gln	Glu	Phe	Gln		Ile	Met
				820	_	_			825					830		
	Tyr	Cys			Phe										Pro	Pro
	_		835													
40	Val		Gln	Gly	Gln	Arg		Ser	Pro	Gly	Ser	Tyr	Pro	Thr	Val	Ile
	_	850					855					860				
		Gln	Gln	Asn	Ala		Ser	Gln	Arg	Ala	Ala	Lys	Asn	Gly	Pro	Pro
	865					870					875					880
	Val	Ser	Asp	Gln	Lys	Glu	Val	Leu	Pro	Ala	Gly	Val	Thr	Ile	Lys	Gln
45					885					890					895	
	Glu	Gln	Asn	Leu	Asp	Gln	Thr	Tyr	Leu	Asp	Asp	Val	Asn	Glu	Ile	Ile
				900					905					910		
	Arg	Lys	Glu	Phe	Ser	Gly	Pro	Pro	Ala	Arg	Asn	Gln	Thr	Arg	Ile	Leu
			915					920					925			
50	Gln	Ser	Thr	Val	Pro	Arg	Ala	Arg	Asp	Pro	Pro	Val	Ala	Thr	Met	Val
		930					935					940				
	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu
	945					950					955					960
	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly
55					965					970					975	
	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr

				980					985					990				
	Thr	Gly	Lys 995	Leu	Pro	Val		Trp	Pro	Thr	Leu		Thr 1005	Thr	Leu	Thr		
5		Gly 1010	Val	Gln	Cys		Ser 1015	Arg	Tyr	Pro		His .020	Met	Lys	Gln	His		
	_	Phe	Phe	Lys			Met	Pro	Glu	_	_	Val	Gln	Glu				
	025 Tle	Phe	Dhe	Lve		L030	Glv	Δen	ጥህም		1035 Thr	Ara	Δla	Glu		1040 Tvs		
	116	FILE	FILE	-	1045	rsp	Gry	VOII	_	.050	1111	AT 9	AIG		.055	Lys		
10	Phe	Glu	_	Asp 1060	Thr	Leu	Val		Arg L065	Ile	Glu	Leu		Gly 1070	Ile	Asp		
	Phe	Lys		Asp	Gly	Asn			Gly	His	Lys			Tyr	Asn	Tyr		
	Δen	Ser	L075 អ.ទ	Δen	Val	Tvr		L080 Met	Δla	Asp	Lvs		1.085 1.vs	Asn	Glv	Ile		
15		1090	1113	AJII	V 4.1		1095	1100	ALG	wob		.100	בין ב		017			
		Val	Asn	Phe	Lys			His	Asn	Ile	Glu	Asp	Gly	Ser	Val	Gln		
	105		_			1110		_			115	~ 3	_	~1		120		
	Leu	Ala	Asp		Tyr 125	GIn	GIn	Asn		Pro 130	TTE	GIY	Asp		Pro .135	val		
20	Leu	Leu	Pro			His	Tyr	Leu			Gln	Ser	Ala			Lys		
				1140					1145					150		-		
	Asp	Pro		Glu	Lys	Arg	_		Met	Val	Leu			Phe	Val	Thr		
	7.1.		1155	<b>71</b> _	mb.sa	T 0.11		L160	7	<b>~</b> 1	T 0		165				د	
25		Ala 1170	GIÀ	пе	Int		G19 1175	Met	Asp	GIU		191	гуз					
			(2)	INF	ORMA	OITA	V FOR	R SE	Q ID	NO: 1	L34:							
						777 R T7 7	CMET											
30		( )	L) SI				2 bas											
							ic ac											
							S: si		<b>=</b>									
			(D)	TOPO	LOG	<i>t</i> : 1:	inear	r										
35		/ -	Li) N	AOI EC	ם וווי	ימעים	r. cr	מזור										
33			ix) I			1121	5: CI	JNA.										
		, ,	, -															
								_	equer	ıce								
40							12											
40			(D)	OIF	1EK	LNFOI	RMAT:	LON:										
		()	ci) S	SEQUE	ENCE	DESC	CRIP	rion	: SE(	Q ID	NO:1	L34:						
	ATG	GTG	AGC	DAG	GGC	GAG	GAG	СТС	ттс	ΔCC	GGG	GTG	GTG	CCC	ATC	CTG	48	
45		Val																
	1			•	5					10	-				15			
		GAG															96	
50	Val	Glu	Leu	Asp 20	GIA	Asp	Val	Asn	G1y 25	His	Lys	Pne	ser	7a1	ser	GIÀ		
50			-	20					. 2 3									
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	144	
	Glu	Gly	Glu	Gly	Asp	Ala	Thr	_	Gly	Lys	Leu	Thr		ГÀЗ	Phe	Ile		
E E			35					40					45					
55	TGC	ACC	ACC	GGC	DAA	СТС	כככ	GTG	כככ	TGG	CCC	ACC	CTC	GTG	ACC	ACC	192	
	100	ACC	ACC		- 14-74			<b>J1 G</b>		200			-10	010				269

270

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
5		ACC Thr															240
10		CAC His															288
45		ACC Thr															336
15		AAG Lys															384
20		GAC Asp 130															432
25		TAC Tyr															480
30		ATC Ile													_		528
0.5		CAG Gln															576
35		GTG Val				-											624
40		AAA Lys 210													_	_	672
45		ACC Thr															720
50·		CTC Leu															768
		CTC Leu			Lys										Leu		816
55	GAC	GAG	CTG	GAG	CTG	GAG	TTG	GAT	CAG	AAG	GAC	GAA	CTG	ATC	CAG	AAG	864

									•	211								
	Asp	Glu	Leu 275	Glu	Leu	Glu	Leu	Asp 280	Gln	Lys	Asp	Glu	Leu 285	Ile	Gln	Lys		
	CTG	CAG	AAC	GAG	CTG	GAC	AAG	TAC	CGC	TCG	GTG	ATC	CGA	CCA	GCC	ACC	4.	912
5	Leu	Gln 290	Asn	Glu	Leu	Asp	Lys 295	Tyr	Arg	Ser	Val	Ile 300	Arg	Pro	Ala	Thr		***
		CAG																960
10	305	Gln	Ala	GIN	гуя	310	ser	Ala	ser	Int	315	GIII	GIY	Gru	PIO	320		
		AAG Lys													_	_		1008
	1111	ביים	*****	0111	325		-			330				<u>L</u> -	335			
15	a » m	CTC	N C C	C7 M	CTC	7.00	CTC	CCC	TT CT CT	<b>Т</b> Л С	aca	7 7 C	אככ	CCN	CAG	TCC		1056
		Leu													_			1030
	-			340					345	_				350				
20	AAG	GAT	CTT	ATA	AAG	GAA	GCT	ATC	CTT	GAC	AAT	GAC	TTT	ATG	AAG	AAC		1104
		Asp																
			355					360					365					
	TTG	GAG	CTG	TCG	CAG	ATC	CAG	GAG	ATT	GTG	GAT	TGT	ATG	TAC	CCG	GTG		1152
25	Leu	Glu	Leu	Ser	Gln	Ile		Glu	Ile	Val	Asp		Met	Tyr	Pro	Val		:
		370					375					380						
		TAT																1200
30	Glu 385	Tyr	Gly	Lys	Asp	Ser 390	Cys	Ile	Ile	Lys	Glu 395	Gly	Asp	Val	GIY	Ser 400		
50																		
		GTG																1248
	Leu	Val	TAL	vai	405	GIU	Asp	GIY	цур	410	GIU	vai	1111	цуз	415	Gry		
35													~~~	<b></b>	mma	a cm		1206
•		AAG Lys																1296
	, , ,	2,5	204	420			1		425	-1-			1	430				
40	א נדילדי	CTT	መአ ር	אאכי	TICIT	N.C.C	ccc	א כי א	GCG	N.C.C	GTC	DAG	ΔСТ	Стт	GTA	דעע		1344
40		Leu																
			435					440					445					
	GTA	AAA	CTC	TGG	GCC	ATT	GAT	CGA	CAA	TGT	TTT	CAA	ACA	ATA	ATG	ATG		1392
45		Lys										Gln						٠
		450					455					460						
	AGG	ACA	GGA	CTC	ATC	AAG	CAT	ACC	GAG	TAT	ATG	GAA	TTT	TTA	AAA	AGC		1440
50		Thr	Gly	Leu	Ile		His	Thr	Glu	Tyr		Glu	Phe	Leu	Lys	Ser 480		
50	465			-		470					475					-100		•
		CCA																1488
	Val	Pro	Thr	Phe	Gln 485	Ser	Leu	Pro	Glu	Glu 490	ıle	ьeu	ser	ьys	Leu 495	Ala		
55																		
	GAT	GTC	CTT	GAA	GAG	ACC	CAC	TAT	GAA	AAT	GGA	GAA	TAT	ATT	ATC	AGG		1536

	Asp	Val	Leu	Glu 500	Glu	Thr	His	Tyr	Glu 505	Asn	Gly	Glu	Tyr	Ile 510	Ile	Arg	
5					GGG Gly											_	1584
10					GAA Glu												1632
					GGA Gly												1680
15					GCA Ala 565												1728
20					GAC Asp												1776
25					GCA Ala						-						1824
30					TTC Phe												1872
					GGA Gly												1920
35					GAA Glu 645												1968
40					GAC Asp												2016
45		_			GGG Gly	_											2064
50					AGC Ser												2112
					TGG Trp												2160
55	TCT	ACA	ACC	AGA	TTT	TAC	ACA	GCA	TGT	GTG	GTA	GAA	GCT	TTT	GCC	TAT	2208

										213								
	Ser	Thr	Thr	Arg	Phe 725	Tyr	Thr	Ala	Cys	Val 730	Val	Glu	Ala	Phe	Ala 735	Tyr		
5	-			AAA Lys 740										_			ેનું 2256 `જે.	-
10				CAC His										_		_	2304	
				GGA Gly													2352	
15				GCC Ala													2400	•
20				TGG Trp												GGC ⁻ Gly	2448	
25				TTC Phe 820													24.96	
30				ATT Ile										_			2544	
25				TTA Leu													2592 ·.	
35				TTG Leu													2640	
40				TTT Phe													2688	
45				CCA Pro 900													2736	
50				GAG Glu													2784	
55				GAC Asp		TAA											280	2

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## (2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 933 amino acids
- (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
  10 (v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

15	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
20	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
25	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
				100					Gly 105					110		
	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
30		130		-		_	135		Ile			140	_			
	145	-				150		_	Ile		155	_				160
35					165				Arg	170					175	
				180					Gln 185					190		
			195					200	Tyr				205			
40		210					215		Asp			220				
	225					230			Gly		235					240
45					245				Gly	250					255	
				260					Leu 265					270		
			275					280	Gln				285			
50		290					295		Arg			300				
	305					310			Ser		315					320
55	Thr	Lys	Arg	Gln	Ala 325	Ile	Ser	Ala	Glu	Pro 330		Ala	Phe	Asp	Ile 335	Gln

Asp Leu Ser His Val Thr Leu Pro Phe Tyr Pro Lys Ser Pro Gln Ser

				340					345					350		
	Lys	Asp	Leu 355	Ile	Lys	Glu	Ala	Ile 360	Leu	Asp	Asn	Asp	Phe 365	Met	Lys	Asn
5	Leu	Glu 370	Leu	Ser	Gln	Ile	Gln 375	Glu	Ile	Val	Asp	Cys 380	Met	Tyr	Pro	Val
-			Gly	Lys	Asp			Ile	Ile	Lys		Gly	Asp	Val	Gly	
	385 Leu	Val	Tyr	Val	Met	390 Glu	Asp	Gly	Lys	Val	395 Glu	Val	Thr	Lys	Glu	400 Gly
10	Val	Lys	Leu	Cys	405 Thr	Met	Gly	Pro	Gly	410 Lys	Val	Phe	Gly	Glu	415 Leu	Ala
		-		420					425 Ala					430		
			435		_		_	440					445			
15		450					455		Gln			460				
	Arg 465	Thr	Gly	Leu	Ile	Lys 470	His	Thr	Glu	Tyr	Met 475	Glu	Phe	Leu	Lys	Ser 480
	Val	Pro	Thr	Phe	Gln 485	Ser	Leu	Pro	Glu	Glu 490	Ile	Leu	Ser	Lys	Leu 495	Ala
20	Asp	Val	Leu			Thr	His	Tyr	Glu 505		Gly	Glu	Tyr	Ile 510		Arg
	Gln	Gly	Ala 515	500 Arg	Gly	Asp	Thr	Phe 520	Phe	Ile	Ile	Ser	Lys 525		Thr	Val
25	Asn			Arg	Glu	Asp			Ser	Glu	Asp	Pro 540		Phe	Leu	Arg
25		530 Leu	Gly	Lys	Gly		535 Trp	Phe	Gly	Glu			Leu	Gln	Gly	
	545 Asp	Val	Arg	Thr		550 Asn	Val	Ile	Ala		555 Glu	Ala	Val	Thr		560 Leu
30	Val	Ile	Asp	Arg	565 Asp	Ser	Phe	Lys	His	570 Leu	Ile	Gly	Gly	Leu	575 Asp	Asp
	Val	Ser	Asn	580 Lys	Ala	Tyr	Glu	Asp	585 Ala	Glu	Ala	Lys	Ala	590 Lys	Tyr	Glu
			595	-		_		600	Leu				605			
35		610					615					620				
	625	_				630			Phe		635			,		640
		-			645		_		Phe	650		_			655	
40	Arg	His	Ile	Val 660	Asp	Thr	Arg	Gln	Gln 665	Glu	His	Ile	Arg	Ser 670	Glu	Lys
	Gln	Ile	Met 675	Gln	Gly	Ala	His	Ser 680	Asp	Phe	Ile	Val	Arg 685	Leu	Tyr	Arg
45	Thr	Phe 690	Lys	Asp	Ser	Lys	Tyr 695	Leu	Tyr	Met	Leu	Met 700	Glu	Ala	Cys	Leu
	Gly 705		Glu	Leu	Trp	Thr 710		Leu	Arg	Asp	Arg 715	Gly	Ser	Phe	Glu	Asp 720
		Thr	Thr	Arg			Thr	Ala	Cys	Val 730		Glu	Ala	Phe	Ala 735	
50	Leu	His	Ser	Lys 740	725 Gly	Ile	Ile	Tyr	Arg 745		Leu	Lys	Pro	Glu 750		Leu
	Ile	Leu	Asp 755		Arg	Gly	Tyr	Ala 760	Lys	Leu	Val	Asp	Phe		Phe	Ala
55	Lys			Gly	Phe	Gly	Lys 775		Thr	Trp	Thr	Phe 780		Gly	Thr	Pro
JJ	Glu	770 Tyr	Val	Ala	Pro	Glu		Ile	Leu	Asn	Lys		His	Asp	Ile	Ser

276

										210							
	785					790					795					800	
	Ala	Asp	Tyr	Trp	Ser 805	Leu	Gly	Ile	Leu	Met 810	Tyr	Glu	Leu	Leu	Thr 815	Gly	
5	Ser	Pro	Pro	Phe 820	Ser	Gly	Pro	Asp	Pro 825	Met	Lys	Thr	Tyr	Asn 830	Ile	Ile	
	Leu	Arg	Gly 835	Ile	Asp	Met	Ile	Glu 840	Phe	Pro	Lys	Lys	Ile 845	Ala	Lys	Asn	
	Ala	Ala 850		Leu	Ile	Lys	Lys 855	Leu	Cys	Arg	Asp	Asn 860	Pro	Ser	Glu	Arg	
10	Leu 865	Gly	Asn	Leu	Lys	Asn 870		Val	Lys	Asp	Ile 875		Lys	His	Lys	Trp 880	
		Glu	Gly	Phe	Asn 885	Trp	Glu	Gly	Leu	Arg 890		Gly	Thr	Leu	Thr 895	Pro	
15	Pro	Ile	Ile	Pro 900		Val	Ala	Ser	Pro 905		Asp	Thr	Ser	Asn 910	Phe	Asp	
	Ser	Phe	Pro 915		Asp	Asn	Asp	Glu 920		Pro	Pro	Asp	Asp 925	Asn	Ser	Gly	
	Trp	Asp 930		Asp	Phe												
20																	
			(2)	INI	FORMA	OITA	V FO	R SE	Q ID	NO: 1	136:						
		( j	i) SI	EQUE	NCE (	CHARA	ACTE	RIST	ICS:								
				LENG													
25				TYP													
				STRA				_	2								
			(D)	TOPO	OLOG	7: 1:	ıneaı	ר									
		(:	ii) N	OLE	CULE	TYPE	E: cl	ANC									
30		( :	ix) I	FEAT	JRE:												
			(3.)		ATT / 151	7V - 7	7 A A	0									
				NAI LO				_	eque	nce							
				OT													
35																	
		()	ci) S	SEQUI	ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	136:					
		GGC												_			48
40		Gly	Thr	Leu		Asp	Leu	Gln	Tyr		Leu	Gln	Glu	Lys		Glu	
40	1				5					10					15		
	GAG	CTG	AGG	CAG	CGG	GAT	GCT	CTC	ATC	GAC	GAG	CTG	GAG	CTG	GAG	TTG	96
	Glu	Leu	Arg	Gln	Arg	Asp	Ala	Leu	Ile	Asp	Glu	Leu	Glu	Leu	Glu	Leu	
4.5				20					25					30			
45	ርስጥ	CAG	አአር	GAC	CAA	СТС	אידיר	CNG	אאכ	СТС	CNG	አአር	GAG	CTG	GAC	ΔAG	144
		Gln															
	-		35	-				40	•				45		_	_	
50	<b>ፐል</b> ር	CGC	דרנ <u>י</u>	GTG	ልጥሮ	CGA	$CC_{\lambda}$	GCC	מככ	CAG	CAG	GCG	CAG	AAC	CVG	AGC	192
30		Arg															172
	-	50				J	55					60		-			
	000	7 C C	7.00	TITE C	C2 C	000	C* ~	000	000	200	7 7 C	aaa	C A C	000	አጥሮ	TCC	240
55																TCC Ser	240
	65					70					75	- 3				80	
																	,

		CCC Pro								_	_	CTG Leu	٠.	288
5 .		TAC Tyr												336
10		GAC Asp 115												384
15		GTG Val												432
20		AAA Lys									_			480
25		GTT Val											,	528
		AAA Lys												576
30	_	ACC Thr 195										GAT Asp		624
35		TGT Cys												_672
40		TAT Tyr		Phe	Leu	Lys	Val	Pro	Thr					720
45		GAG Glu												768
		AAT Asn												816
50		ATC Ile 275												864
55		GAA Glu												912

	•								
5	GGA Gly							_	960
Ū	GCT Ala								1008
10	CAT His								1056
15	GCA Ala							_	1104
20	CTG Leu 370								1152
25	TTC Phe						_		1200
·	TTT Phe								1248
30	CAG Gln							CAT His	1296
35	GAT Asp								1344
40	TAT Tyr 450								1392
45	AGG Arg								1440
	TGT Cys				 			_	1488
50	AGG Arg								1536
55	AAA Lys								1584

5	 ACA Thr 530							_	1632
•	CTG Leu							_	1680
10	CTA Leu								1728
15	CCT Pro								1776
20	TTT Phe								1824
25	TGC Cys 610								1872
	AAA Lys							_	1920
30	TTA Leu								1968
35	CCC Pro								2016
40	CCA Pro								2064
45	CCG Pro 690								2112
	GTG Val								2160
50	AGC Ser								2208
55	CTG Leu								2256

PCT/DK98/00145 WO 98/45704

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5			ACC Thr											2304
3			ATG Met											2352
10			CAG Gln											2400
15			GCC Ala									_		2448
20			AAG Lys 820											2496
25			GAG Glu											2544
20			AAG Lys											2592
30			GGC Gly											2640
35			GAC Asp											2688
40			GCC Ala 900											2736
45			GAG Glu					Ala					GAC Asp	2784
40	CTG Leu 930		AA ( Lys	GTAA										2799
50		(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	137:				

- (2) INFORMATION FOR SEQ ID NO:137:
- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 932 amino acids
- (B) TYPE: amino acid
  - (C) STRANDEDNESS: single

281

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

			,													
	Met 1	Gly	Thr	Leu	Arg 5	Asp	Leu	Gln	Tyr	Ala 10	Leu	Gln	Glu	Lys	Ile 15	Glu
10	Glu	Leu	Arg	Gln 20	Arg	Asp	Ala	Leu	Ile 25	Asp	Glu	Leu	Glu	Leu 30	Glu	Leu
	Asp	Gln	Lys 35	Asp	Glu	Leu	Ile	Gln 40	Lys	Leu	Gln	Asn	Glu 45	Leu	Asp	Lys
15	Tyr	Arg 50	Ser	Val	Ile	Arg	Pro 55	Ala	Thr	Gln	Gln	Ala 60	Gln	Lys	Gln	Ser
	65		Thr			70			_		75	_				80
			Pro		85					90					95	
20			Tyr	100	-				105					110		
			Asp 115		_			120					125			
25		130	Val				135					140				
	145		Lys		_	150		_			155	_				160
	_	-	Val		165		_		_	170	_				175	
30		•	Lys	180					185					190		
			Thr 195		_			200			_		205			
35		210	Cys				215					220				
	225		Tyr			230					235					240
40			Glu		245					250					255	
40	-		Asn	260					265					270		
			11e 275					280					285			
45		290	Glu				295					300				
	305		Glu			310					315					320
50			Ala		325					330					335	
50	_		Leu	340					345	_				350	_	
	-		Glu 355	-	_		_	360					365			
55		370	Lys				375					380				
	Gly	Phe	Gly	Arg	Val	Glu	Leu	Val	Gln	Leu	Lys	Ser	Glu	Glu	Ser	Lys

	385					390					395					400
	Thr	Phe	Ala	Met	Lys 405	Ile	Leu	Lys	Lys	Arg 410	His	Ile	Val	Asp	Thr 415	Arg
5	Gln	Gln	Glu	His		Arg	Ser	Glu	Lys 425		Ile	Met	Gln	Gly 430		His
Ū	Ser	Asp	Phe		Val	Arg	Leu	Tyr 440		Thr	Phe	Lys	Asp		Lys	Tyr
	Leu	Tyr 450	Met	Leu	Met	Glu	Ala 455		Leu	Gly	Gly	Glu 460	Leu	Trp	Thr	Ile
10	Leu 465		Asp	Arg	Gly	Ser 470		Glu	Asp	Ser	Thr 475	Thr	Arg	Phe	Tyr	Thr 480
		Cys	Val	Val	Glu 485	Ala	Phe	Ala	Tyr	Leu 490	His	Ser	Lys	Gly	Ile 495	Ile
15	Tyr	Arg	Asp	Leu 500	Lys	Pro	Glu	Asn	Leu 505	Ile	Leu	Asp	His	Arg 510	Gly	Tyr
	Ala	Lys	Leu 515	Val	Asp	Phe	Gly	Phe 520	Ala	Lys	Lys	Ile	Gly 525	Phe	Gly	Lys
	Lys	Thr 530	Trp	Thr	Phe	Cys	Gly 535	Thr	Pro	Glu	Tyr	Val 540	Ala	Pro	Glu	Ile
20	545		Asn	_		550					555					560
			Met	-	565					570					575	
25			Met	580					585					590		
	Glu	Phe	Pro 595	Lys	Lys	Ile	Ala	Lys 600	Asn	Ala	Ala	Asn	Leu 605	Ile	Lys	Lys
		610	Arg	_			615					620				
30	625		Asp			630		_			635					640
	_		Arg	-	645					650					655	
35			Thr	660					665					670		
			Pro 675		_	-		680	_	_	_		685			
40		690	Val				695		-	-		700				
40	705					710			_	_	715					T 20
			Val		725		_		_	730					735	
45			Lys	740					745					750		
			Val 755					760	_			_	765			
50		770					775					780				Glu
50	785	-				790					795	_	_	_		Tyr 800
			_		805					810	_				815	Arg Gly
55				820					825					830		Ala
	1113	-ys	Leu		- y -	LO II	- y L	UDII		1113	11011	· uı	- Y L	115		

	Asp	Lvs	835 Gln	Lys	Asn	Gly	Ile	840 Lys	Val	Asn	Phe	Lys	845 Ile	Arg	His	Asn		
	-	850		Gly			855					860				•	•	
5	865		_	Asp		870					875					880	٠.	
					885					890					895			
				Ala 900					905					910				
10			915	Glu	Phe	Val	Thr	Ala 920	Ala	GIY	Ile	Thr	1eu 925	GIY	Met	Asp		
	Glu	Leu 930	Tyr	Lys														
15			(2)	INI	ORM	OITA	1 FOE	SEÇ	) ID	NO: 1	138:							
20		(1	(A) (B) (C)	EQUEN LENC TYPI STRA	ETH: E: nu ANDEI	2184 cle: ONES	bas ic ac	se pa cid ingle	airs									
25		•		OLEC FEATU		TYPI	E: cI	ANC									į	
20			(B)	NAM LOC OTI	CATIO	: ИС	12	2181	equei	nce								
30		(:	xi) S	SEQUI	ENCE	DES	CRIP	rion	: SE	Q ID	NO:	138:						
				AAG Lys													.48	
35				GAC Asp 20													96	
40				GGC Gly													144	
45				GGC Gly													192	
50				GGC Gly													240	
55				TTC Phe													288	ı
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	283

284

										204							
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
5		AAG Lys															384
10		GAC Asp 130															432
15		TAC Tyr															480
13		ATC Ile															528
20		CAG Gln															576
25		GTG Val															624
30		AAA Lys 210															672
35		ACC Thr															720
00		CTC Leu															768
40		TGG Trp															816
45		TTC Phe															864
50		CAG Gln 290															912
55		CAG Gln															960
55	ATC	ATC	CGC	TGC	CTG	CAG	TGG	ACC	ACT	GTC	ATC	GAA	CGC	ACC	TTC	CAT	1008

										285								
	Ile	Ile	Arg	Cys	Leu 325	Gln	Trp	Thr	Thr	Val 330	Ile	Glu	Arg	Thr	Phe 335	His		
5						GAG Glu											1056	
10						AAG Lys											1104	
15						GAC Asp											1152	
15						CAC His 390											1200	
20						GGC Gly											1248	
25						TAC Tyr											1296	
30						GAG Glu										_	1344	
35						CAC His											1392	
33						CTC Leu 470										GGC Gly 480	1440	
40						CTG Leu											1488	
45						GCT Ala											1536	
50						GTG Val											1584	
						CAC His											1632	
55	GAG	GGG	ATC	AAG	GAC	GGT	GCC	ACC	ATG	AAG	ACC	TTT	TGC	GGC	ACA	CCT	1680	28

	Glu 545	Gly	Ile	Lys	Asp	Gly 550	Ala	Thr	Met	Lys	Thr 555	Phe	Cys	Gly	Thr	Pro 560	
5		TAC Tyr														_	1728
10		GAC Asp															1776
		CTG Leu															1824
15		ATG Met 610															1872
20		TTG Leu															1920
25		GGC Gly															1968
30		ATC Ile															2016
25		CCC Pro															2064
35		ACG Thr 690														AGC Ser	2112
40		GAG Glu										Phe					2160
45		TCG Ser															2184
50			(2	) IN	FORM	ATIO	и го	R SE	Q ID	NO:	139:						
00		(	(A)	LEN	NCE GTH:	727	ami	no a									
55			(C)	STR	E: a ANDE OLOG	DNES	S: s	ingl	e								

287

(ii) MOLECULE TYPE: protein
(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

_		()	(1)	SEQUE	SNCE	DESC	LRIP	LION	SEC	ם דם	NO:	139:				
5	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
10		_	35					Tyr 40	_	_			45	_		
	_	50					55	Val				60				
15	65		_	_		70	_	Phe		_	75		-			80
			_		85	-		Ala		90		_	_		95	
00				100				Asp	105					110		
20		_	115			_		Leu 120					125			
		130					135	Asn			_	140				
25	145	_				150		Tyr			155	_	_			160
	_		_		165		_	Ile Gln	_	170					175	
30				180			_	His	185					190		
30			195					200 Arg	-				205			
		210					215	Leu				220				
35	225					230		Met	_		235					240
	_		_		245	_		Glu		250					255	
40				260				Gly	265					270		
	_		275					280 Glu					285			
		290	•		_		295	Thr				300				
45	305 Ile	Ile	Arg	Cys	Leu	310 Gln	Trp	Thr	Thr	Val	315 Ile	Glu	Arg	Thr	Phe	320 His
	Val	Glu	Thr	Pro	325 Glu	Glu	Arg	Glu	Glu	330 Trp	Thr	Thr	Ala	Ile	335 Gln	Thr
50	Val	Ala	Asp	340 Gly	Leu	Lys	Lys	Gln	345 Glu	Glu	Glu	Glu	Met	350 Asp	Phe	Arg
	Ser	Gly	355 Ser	Pro	Ser	Asp	Asn	360 Ser	Gly	Ala	Glu	Glu	365 Met	Glu	Val	Ser
	Leu	370 Ala	Lys	Pro	Lys	His	375 Arg	Val	Thr	Met	Asn	380 Glu	Phe	Glu	Tyr	Leu
55	385 Lys	Leu	Leu	Gly	Lys	390 Gly	Thr	Phe	Gly	Lys	395 Val	Ile	Leu	Val	Lys	400 Glu

10   Glu Leu Phe Phe His Leu Ser Arg Glu Arg Val Phe Ser Glu Asp 485   490   495											200						
11e Val Ala Lys Asp Glu Val Ala His Thr Leu Thr Glu Asn Arg Val Ala Lys Asp Glu Val Ala His Thr Leu Thr Glu Asn Arg Val Aso Associated the second of the s						405					410					415	
Tile Val Ala Lys Asp Glu Val Ala His Thr Leu Thr Glu Asn Arg Val Ala Ala Lys Syr Ser Leu Gln Asn Ser Arg His Pro Phe Leu Thr Ala Leu Lys Tyr Ser Ala Con Aso Ser Arg His Pro Phe Leu Thr Ala Leu Lys Tyr Ser Ala Con Aso Arg Val Ala Asn Gly Glu Thr His Asp Arg Leu Cys Phe Val Met Glu Tyr Ala Asn Gly Glu Cys Phe Phe His Leu Ser Arg Glu Arg Val Phe Ser Glu Asp Ala Arg Phe Tyr Gly Ala Glu Tie Val Ser Ala Leu Asp Tyr Leu Sor Sos Sos Ser Glu Lys Asn Val Val Tyr Arg Asp Leu Lys Leu Glu Asn Leu Sos		Lys	Ala	Thr	_	Arg	Tyr	Tyr	Ala		Lys	Ile	Leu	Lys		Glu	Val
Leu Gln Asn Ser Arg His Pro Phe Leu Thr Ala Leu Lys Tyr Ser 1 450  Gln Thr His Asp Arg Leu Cys Phe Val Met Glu Tyr Ala Asn Gly Glu Leu Phe Phe His Leu Ser Arg Glu Arg Val Phe Ser Glu Asp Ap5  Ala Arg Phe Tyr Gly Ala Glu Ile Val Ser Ala Leu Asp Tyr Leu Sono  Ser Glu Lys Asn Val Val Tyr Arg Asp Leu Lys Leu Glu Asn Leu Sono  Ser Glu Lys Asn Val Val Tyr Arg Asp Leu Lys Leu Glu Asn Leu Sono  Glu Gly Ile Lys Asp Gly His Ile Lys Ile Thr Asp Phe Gly Leu Cys Sono  Glu Gly Ile Lys Asp Gly Ala Thr Met Lys Thr Phe Cys Gly Thr Sono  Glu Gly Ile Lys Asp Gly Ala Thr Met Lys Thr Phe Cys Gly Thr Sono  Glu Tyr Leu Ala Pro Glu Val Leu Glu Asp Asn Asp Tyr Gly Arg Sono  Arg Leu Pro Phe Tyr Asn Gln Asp His Glu Lys Leu Phe Glu Leu Sono  Arg Leu Ber Gly Leu Leu Lys Lys Asp Pro Leu Gly Pro Glu Ala Sono  Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe Glo Sono  Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe Glo Sono  Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe Glo Sono  Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe Glo Sono  Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe Glo Sono  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu Gono  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705  (2) INFORMATION FOR SEQ ID NO:140:  45  (1) SEQUENCE CHARACTERISTICS:  (2) INFORMATION FOR SEQ ID NO:140:		Ile	Val			Asp	Glu	Val			Thr	Leu	Thr			Arg	Val
450   455   460   460   465   470   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475   475	5		_			_	•	_		_			_		_	<b>.</b>	<b>5</b> 1
465 Glu Leu Phe Phe His Leu Ser Arg Glu Arg Val Phe Ser Glu Asp Ads 5 490  Ala Arg Phe Tyr Gly Ala Glu Ile Val Ser Ala Leu Asp Tyr Leu 1500  Ser Glu Lys Asn Val Val Tyr Arg Asp Leu Lys Leu Glu Asn Leu Sil 515  Leu Asp Lys Asp Gly His Ile Lys Ile Thr Asp Phe Gly Leu Cys 150  Glu Gly Ile Lys Asp Gly Ala Thr Met Lys Thr Phe Cys Gly Thr 545  Glu Gly Ile Lys Asp Gly Ala Thr Met Lys Thr Phe Cys Gly Thr 545  Office Glu Tyr Leu Ala Pro Glu Val Leu Glu Asp Asn Asp Tyr Gly Arg 565  Val Asp Trp Trp Gly Leu Gly Val Val Met Tyr Glu Met Met Cys 655  Arg Leu Pro Phe Tyr Asn Gln Asp His Glu Lys Leu Phe Glu Leu 615  Leu Met Glu Glu Ile Arg Phe Pro Arg Thr Leu Gly Pro Glu Ala 1665  Ser Leu Leu Ser Gly Leu Leu Lys Lys Asp Pro Lys Gln Arg Leu 625  Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe 6365  Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro 665  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 670  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 690  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705  (2) INFORMATION FOR SEQ ID NO:140:		Leu		Asn	Ser	Arg	His		Phe	Leu	Thr	Ala		Lys	Tyr	ser	Pne
10   Glu Leu Phe Phe His Leu Ser Arg Glu Arg Val Phe Ser Glu Asp 485   485   490   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495   495			Thr	His	Asp	Arg		Cys	Phe	Val	Met		Tyr	Ala	Asn	Gly	Gly 480
Ala Arg Phe Tyr Gly Ala Glu Ile Val Ser Ala Leu Asp Tyr Leu 1500 500 505 510 510 510 510 505 505 510 510	10		Leu	Phe	Phe			Ser	Arg	Glu	_		Phe	Ser	Glu		Arg
15		Ala	Arg	Phe	-		Ala	Glu	Ile			Ala	Leu	Asp			His
Glu Gly Ile Lys Asp Gly Ala Thr Met Lys Thr Phe Cys Gly Thr 545  20 Glu Tyr Leu Ala Pro Glu Val Leu Glu Asp Asn Asp Tyr Gly Arg 565  Val Asp Trp Trp Gly Leu Gly Val Val Met Tyr Glu Met Met Cys 605  Arg Leu Pro Phe Tyr Asn Gln Asp His Glu Lys Leu Phe Glu Leu 610  Ser Leu Met Glu Glu Ile Arg Phe Pro Arg Thr Leu Gly Pro Glu Ala 610  Ser Leu Leu Ser Gly Leu Lys Lys Asp Pro Lys Gln Arg Leu 625  Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe 665  Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro 660  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 685  Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp 690  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705  (2) INFORMATION FOR SEQ ID NO:140:  45 (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 2394 base pairs  (B) Type: nucleic acid	15	Ser	Glu	-	Asn	Val	Val	Tyr		Asp	Leu	Lys	Leu		Asn	Leu	Met
545		Leu	_	Lys	Asp	Gly	His		Lys	Ile	Thr	Asp		Gly	Leu	Cys	Lys
Secondary   Seco			Gly	Ile	Lys	Asp	_	Ala	Thr	Met	Lys		Phe	Cys	Gly	Thr	Pro 560
25	20	Glu	Tyr	Leu	Ala		Glu	Val	Leu	Glu		Asn	Asp	Tyr	Gly		Ala
Arg Leu Pro Phe Tyr Asn Gln Asp His Glu Lys Leu Phe Glu Leu 595 600 605  Leu Met Glu Glu Ile Arg Phe Pro Arg Thr Leu Gly Pro Glu Ala 610 615 620  Ser Leu Leu Ser Gly Leu Leu Lys Lys Asp Pro Lys Gln Arg Leu 625 630 635  30 Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe 645 655  Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro 655  Gly Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 665  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 685  Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp 690 695 700  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705 710 715  40 Tyr Ser Ala Ser Ser Thr Ala 725  (2) INFORMATION FOR SEQ ID NO:140:		Val	Asp	Trp	_	Gly	Leu	Gly	Val		Met	Tyr	Glu	Met		Cys	Gly
Leu Met Glu Glu Ile Arg Phe Pro Arg Thr Leu Gly Pro Glu Ala 610 615 620  Ser Leu Leu Ser Gly Leu Leu Lys Lys Asp Pro Lys Gln Arg Leu 625 630 635  30 Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe 645 650 655  Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro 660 665 670  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 685  Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp 690 695 700  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705 710 715  40 Tyr Ser Ala Ser Ser Thr Ala 725  (2) INFORMATION FOR SEQ ID NO:140:  45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2394 base pairs (B) TYPE: nucleic acid	25	Arg	Leu		-	Tyr	Asn	Gln		His	Glu	Lys	Leu		Glu	Leu	Ile
Ser Leu Leu Ser Gly Leu Leu Lys Lys Asp Pro Lys Gln Arg Leu 625 630 635  30 Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe 645 655  Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro 660 665 670  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 685  Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp 690 695 700  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705 710 715  40 Tyr Ser Ala Ser Ser Thr Ala 725  (2) INFORMATION FOR SEQ ID NO:140:	20	Leu			Glu	Ile	Arg			Arg	Thr	Leu			Glu	Ala	Lys
30 Gly Gly Ser Glu Asp Ala Lys Glu Ile Met Gln His Arg Phe Phe . 645 650 655  Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro . 660 665 670  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu . 675 680 685  Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp . 690 695 700  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe . 705 710 715  40 Tyr Ser Ala Ser Ser Thr Ala . 725  (2) INFORMATION FOR SEQ ID NO:140:  45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2394 base pairs (B) TYPE: nucleic acid				Leu	Ser	Gly			Lys	Lys	Asp			Gln	Arg	Leu	Gly 640
Gly Ile Val Trp Gln His Val Tyr Glu Lys Lys Leu Ser Pro Pro 660 660 665 670  Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 675 680 685  Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp 690 695 700  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705 710 715  40 Tyr Ser Ala Ser Ser Thr Ala 725  (2) INFORMATION FOR SEQ ID NO:140:  45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2394 base pairs (B) TYPE: nucleic acid	30		Gly	Ser	Glu	_		Lys	Glu	Ile			His	Arg	Phe		
Lys Pro Gln Val Thr Ser Glu Thr Asp Thr Arg Tyr Phe Asp Glu 675 680 685  Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp 690 695 700  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705 710 715  40 Tyr Ser Ala Ser Ser Thr Ala 725  (2) INFORMATION FOR SEQ ID NO:140:  45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2394 base pairs (B) TYPE: nucleic acid		Gly	Ile	Val	_		His	Val	Tyr			Lys	Leu	Ser			Phe
Phe Thr Ala Gln Met Ile Thr Ile Thr Pro Pro Asp Gln Asp Asp 690 695 700  Met Glu Cys Val Asp Ser Glu Arg Arg Pro His Phe Pro Gln Phe 705 710 715  40 Tyr Ser Ala Ser Ser Thr Ala 725  (2) INFORMATION FOR SEQ ID NO:140:  45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2394 base pairs (B) TYPE: nucleic acid	35	Lys	Pro			Thr	Ser	Glu			Thr	Arg	Tyr			Glu	Glu
705 710 715 40 Tyr Ser Ala Ser Ser Thr Ala 725  (2) INFORMATION FOR SEQ ID NO:140:  45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 2394 base pairs (B) TYPE: nucleic acid		Phe			Gln	Met	Ile		Ile	Thr	Pro	Pro		Gln	Asp	Asp	Ser
725  (2) INFORMATION FOR SEQ ID NO:140:  45  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 2394 base pairs  (B) TYPE: nucleic acid		Met 705	Glu	Cys										Pro	Gln	Phe	Ser 720
45 (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 2394 base pairs  (B) TYPE: nucleic acid	40	Tyr	Ser	Ala	Ser		Thr	Ala									
(A) LENGTH: 2394 base pairs (B) TYPE: nucleic acid				(2	) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	140:					
(B) TYPE: nucleic acid	45		(														
										airs							
(C) STRANDEDNESS: single										e							
(D) TOPOLOGY: linear 50	50			(D)	TOP	oLog	Y: 1	inea	r								

- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
  - (A) NAME/KEY: Coding Sequence
- 55 (B) LOCATION: 1...2391
  - (D) OTHER INFORMATION:

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## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

		•	-	_						-							
5		GAC Asp															48
10		GGC Gly															96
15		TTC Phe															144
10		AGG Arg 50															192
20		TAC Tyr															240
25		CCT Pro															288
30		GGC Gly															336
35		CAG Gln													_	_	384
		ATC Ile 130	Ser												_		432
40		GAA Glu															480
45		CAG Gln															528
50		GTC Val							_								576
55		CTC Leu															624
·	GGG	GAT	GAG	ATC	TTC	CTA	CTG	TGT	GAC	AAG	GTG	CAG	AAA	GAG	GAC	ATT	672 2

	Gly	Asp 210	Glu	Ile	Phe	Leu	Leu 215	Cys	Asp	Lys	Val	Gln 220	Lys	Glu	Asp	Ile	
5		GTG Val															720
10		GCT Ala															768
		GCA Ala													_		816
15		CGG Arg															864
20		CCA Pro 290															912
25		TAT Tyr															960
30		ACC Thr															1008
35		TCA Ser															1056
33		TCC Ser															1104
40		TCT Ser 370															1152
45		GTC Val															1200
50		GCT Ala														_	1248
55		CCT Pro														GGG Gly	1296
JJ	GAA	GGA	ACG	CTG	TCA	GAG	GCC	CTG	CTG	CAG	CTG	CAG	TTT	GAT	GAT	GAA	1344

										231							
	Glu	Gly	Thr 435	Leu	Ser	Glu	Ala	Leu 440	Leu	Gln	Leu	Gln	Phe 445	Asp	Asp	Glu	
	CAC	CTC	ccc	GCC	TTC	СТТ	ccc	אאכ	NGC.	א כי א	GNC	CCA	CCT	ara	TTC	מכמ	~ 1392
5			Gly												Phe		
	GAC	CTG	CCA	TCC	GTC	GAC	ממכ	TCC	GAG	ተጥተ	CAG	CAG	СТС	СТС	AAC	CAG	1440
															Asn		1110
10	465					470					475					480	
	GGC	ATA	CCT	GTG	GCC	CCC	CAC	ACA	ACT	GAG	CCC	ATG	CTG	ATG	GAG	TAC	1488
	Gly	Ile	Pro	Val	Ala	Pro	His	Thr	Thr	Glu	Pro	Met	Leu	Met	Glu	Tyr	
					485					490					495		
15																	
															CCC		1536
	Pro	Glu	Ala		Thr	Arg	Leu	Val		Gly	Ala	Gln	Arg		Pro	Asp	
				500					505					510			
20		~~~	~~~	~~~	~~~	cm a	~~~	000	~~~	~~~	ama	666	2 2 4	-	CTC.	amm	1504
20															CTC		1584
	Pro	Ala		Ala	PIO	Leu	GIY		PIO	GTÅ	Leu	PIO	525	GIY	Leu	Leu	
			515					520					525				
	ייר א	GGA	CAT	GAA	GAC	ጥጥር	тсс	שככ	ידידע	GCG	GAC	ΔТС	GAC	ידידירי	TCA	GCC	1632
25															Ser		1032
20	561	530	YPP	JIU	nsp	1110	535	DCI	110	niu	rop	540	пор		001		
		330					333					3.0					
	CTG	CTG	AGT	CAG	ATC	AGC	TCC	TTG	GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	1680
															Met		
30	545					550			-		555					560	
	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	1728
	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	
					565					570					575		
35																	
															GAG		1776
	Leu	Asp	Gly		Val	Asn	GIA	His		Phe	Ser	Val	Ser		Glu	GIY	
				580					585					590			
40	GNG	ccc	CAT	aaa	א כיכי	<b>ፕ</b> አር	ccc	λλG	стс	אככ	CTC	λλC	ጥጥር	አጥር	TGC	ACC	1824
40															Cys		1024
	Giu	Gry	595	на	1111	TYL	Gry	600	пец	1111	пец	цуз	605	110	Cys	1111	
			,,,					000					005				
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					645					650					655		
55	<b>.</b>			<b>.</b>	<b>~</b>	<b></b>							~~-	<b></b> -			
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40		(:	(A) (B) (C)	EQUEI LENG TYPI STRA	GTH: E: ar ANDEI	797 mino ONES	amin acio S: s:	no ao i ingle	cids								
45		7)	/) FI	MOLE(	ENT 1	TYPE	: in	terna	al	. *B	NO.	. 47 .					
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	225		_	,		230	<b>a</b> 1 -	** . 1		<b>~</b> 7 -	235	D1	3	m\	D	240	
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	~3	370	<b>.</b>		<b>01</b>		375		D		D	380	D	7 J -	M ~ +-	777	
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                              775
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              (C) STRANDEDNESS: single
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              (D) TOPOLOGY: linear
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               (B) LOCATION: 1...2391
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
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30												AGC Ser		TAA			2394
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40		-	ii)	TOP MOLE RAGM	CULE	TYP	E: p	rote									
45		,	•	SEQU													
	1			-	5					10	-				15	Leu	
50			Glu	20	_			Tyr	25		_		Leu	30		Ile	
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	GIN	. nls	Asp	Pne	File	пλг	ser	мта	. Met	. Pro	. G10	. стХ	ıyr	val	GIL	Glu	20

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					85					90					95	
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## **CLAIMS**

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- 1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution to the degree of the influence on the cellular response.
- 2. A method according to claim 1, as used for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact living cell or cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cell or cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information about the spatially distributed light and correlating the quantitative information to the degree of the influence on the intracellular pathway.
  - 3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.
- 4. A method according to any of the preceding claims, wherein the influence is contact between the mechanically intact living cell or the group of mechanically intact living cells with a

chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance.

- 5. A method according to claim 4 wherein the substance is a substance whose effect on anintracellular pathway is to be determined.
  - 6. A method according to any of the preceding claims, wherein the recording is made at a single point in time after the application of the influence.
- 7. A method according to any of claims 1-5, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.
  - 8. A method according to any of claims 1-5, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

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- 9. A method according to any of claims 1-7, wherein the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.
- 25 10. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence.

- 11. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.
- 12. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.
- 13. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.
- 14. A method according to any of claims 1-13, wherein the luminophore is a luminophore which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.
  - 15. A method according to any of claims 1-13, wherein the variation or result with respect to the spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.
  - 16. A method according to claim 15, wherein the change in the intensity of the emission from the luminophore is sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion

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17. A method according to any of claims 1-16, wherein the property of the light being recorded is intensity, fluorescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

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- 18. A method according to any of claims 1-15 or 17, wherein the recording of the spatially distributed light is performed using a recording system which records the spatial distribution of a recordable property of the light in the form of an ordered array of values.
- 19. A method according to claim 18, wherein the recording of the spatial distribution of the recordable property of the light is performed using a charge transfer device such as a CCD array or a vacuum tube device such as a vidicon tube.
  - 20. A method according to any of the preceding claims, wherein the light to be measured passes through a filter which selects the desired component of the light to be measured and rejects other components.
  - 21. A method according to any of the preceding claims, wherein the recording of the spatial distribution of the recordable property of light is performed by fluorescence microscopy.

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- 22. A method according to any of the preceding claims, wherein the recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures.
- 23. A method according to any of claims 2-22, wherein the

- 24. A method according to any of the preceding claims, wherein the luminophore is a fluorophore.
- 5 25. A method according to any of the preceding claims wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells.
- 26. A method according to any of the preceding claims, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.
- 27. A method according to claim 26, wherein the luminescent polypeptide is a GFP as de-
  - 28. A method according to claim 27 wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.
- 29. A method according to claim 28 wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.
  - 30. A method according to any of the previous claims for detecting intracellular translocation of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising
    - a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

- b) modulating the activity of the biologically active polypeptide by incubating the cell or cells with a substance having biological activity and
- c) measuring the fluorescence produced by the incubated cell or cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the translocation of a biologically active polypeptide in said cell.
- 31. A method according to claim 30, wherein the nucleotide sequence is a DNA sequence.
- 32. A method according to claim 30 or 31, wherein the modulation is an activation.

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- 33. A method according to claim 30 or 31, wherein the modulation is a deactivation.
- 34. A method according to any of claims 30-33 wherein the fluorescence of the cell or cells is measured prior to the modulation, and the result or variation determined in step (c) is a change in fluorescence compared to the fluorescence measured prior to the modulation.
- 35. A method according to any of claims 30-34, wherein the intracellular processes are intracellular signalling pathways.
- 36. A method according to claim 34, wherein the change in fluorescence measured in step(c) comprises determining a change in the spatial distribution of the fluorescence.
  - 37. A method according to any of the preceding claims wherein the mechanically intact living cell or cells is/are a mammalian cell/mammalian cells which, during the time peroid over which the influence is observed, is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

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- 38. A method according to any of the preceding claims, wherein the at least one mechanically intact living cell is part of a matrix of identical or non-identical cells.
- 39. A method according to any of claims 1-36 and 38, wherein the cell or cells is/are selected from the group consisting of fungal cells, such as a yeast cell; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.
  - 40. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, with the proviso that the construct is not a construct coding for a fusion polypeptide in which the biologically active polypeptide is selected from the group consisting of PKC-alpha, PKC-gamma, and PKC-epsilon.
- 41. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.
  - 42. A nucleic acid construct according to claim 40 or 41, wherein the biologically active polypeptide is a protein kinase or a phosphatase.
  - 43. A nucleic acid construct according to any of claims 40-42 wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- 44. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

- 45. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
- 46. A nucleic acid construct according to any of claims 40-43, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.
- 47. A nucleic acid construct according to claim 46, wherein the protein kinase is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation
  upon activation.
  - 48. A nucleic acid construct according to claim 46, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - 49. A nucleic acid construct according to claim 46, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- 50. A nucleic acid construct according to claim 46, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 51. A nucleic acid construct according to claim 50 which codes for a PKAc-F64L-S65T-GFP fusion.
  - 52. A nucleic acid construct according to claim 46, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

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53. A nucleic acid construct according to claim 46, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

- 54. A nucleic acid construct according to claim 46, wherein the protein kinase is a mitogenactivated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 55. A nucleic acid construct according to claim 54, which codes for an ERK1-F64L-S65T-GFP fusion.
  - 56. A nucleic acid construct according to claim 54, which codes for an EGFP-ERK1 fusion.
- 57. A nucleic acid construct according to claim 46, wherein the protein kinase is a cyclindependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 58. A nucleic acid construct according to claim 42 or 43, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.
  - 59. A nucleic acid construct according to any of claims 40-58 which is a DNA construct.
- 60. A nucleic acid construct according to any of claims 40-59 wherein the gene encoding GFP is derived from Aequorea victoria.
  - 61. A nucleic acid construct according to claim 60 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

62. A nucleic acid construct according to claim 60 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

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- 63. A DNA construct according to claim 59 and 61 or, where applicable, 62, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, and 142, or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.
- 64. A cell containing a nucleic acid construct according to any of claims 40-63 and capable of expressing the sequence encoded by the construct.

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- 65. A cell according to claim 64, which is a eukaryotic cell.
- 66. A cell according to claim 64, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.
- 67. A cell according to claim 66, which is a mammalian cell.
- 68. An organism carrying in at least one of its component cells a nucleic acid sequence as contained in the constructs according to any of claims 40-59, said cell being capable of expressing said nucleic acid sequence.
  - 69. An organism according to claim 68 which is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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- 70. A fluorescent probe comprising a GFP which is N- or C-terminally tagged, optionally via a peptide linker, to a biologically active polypeptide or a part or a subunit thereof which is a component of a intracellular signalling pathway as defined herein, the probe being a probe which is encoded by the nucleic acid construct according to any of claims 40-59.
- 71. A method according to any of claims 1-39, wherein the luminophore is a fusion polypeptide as encoded by the nucleic acid construct according to any of claims 40-63.
- 72. A method according to any of claims 1-39 or 71 in which the method of the invention is used in a screening program as defined herein.
  - 73. An apparatus for measuring the distribution of fluorescence in at least one cell, and thereby any change in the distribution of fluorescence in at least one cell, which includes the following component parts: (a) a light source, (b) a means for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a means for rapidly blocking or pass ing the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

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- 74. An apparatus according to claim 73 in which some or all of the system is automated.
- 75. An apparatus according to claim 73 in which components d and e comprise a fluorescence microscope.

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76. An apparatus according to claim 73 in which component f is a CCD camera.

77. An apparatus according to claim 73 in which the image is formed and recorded by an optical scanning system.

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- 78. An apparatus according to claim 73 in which a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance.
- 79. An apparatus according to claim 78 in which the liquid addition system is under the control of the computer or electronic system.
  - 80. A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

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- 81 A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.
- 82. A method according to any of claims 1-80 wherein a fluorescent probe is used in backtracking of signal transduction pathways as defined herein.

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- 83. A method of treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method according to the invention.
- 84. A compound that modulates a component of an intracellular pathway as defined herein, as determined by a method according to the method of the invention.
- 10 85. A medical composition comprising a therapeutic amount of a compound identified according the method of the invention.
  - 86. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cell or cells from said patient, transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said patient.
- 87. A method according to any of claims 1-80 of identifying a drug target among the group of biologically active polypeptides which are components of intracellular signalling pathways.

Fig 1

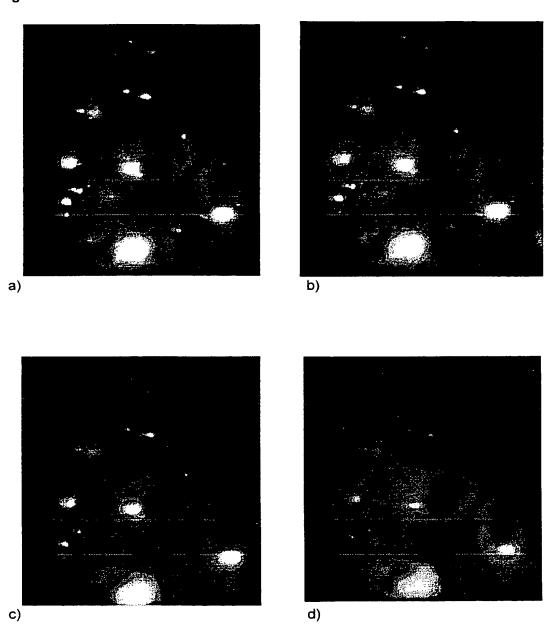


Fig 2

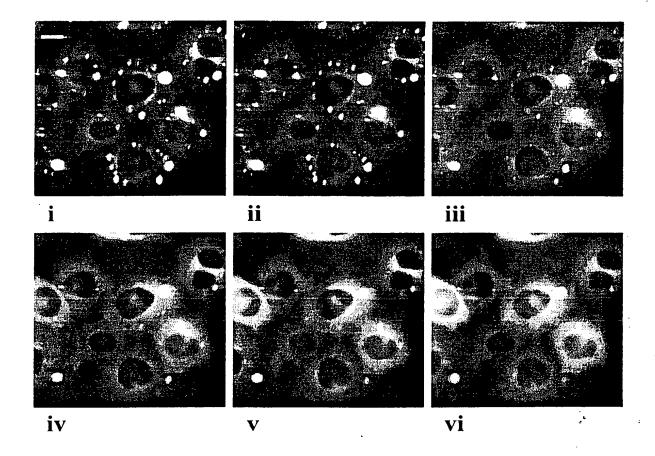
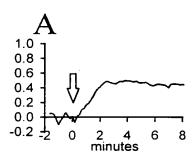
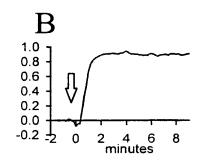
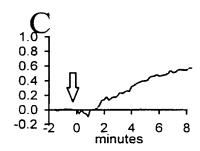
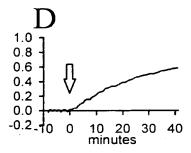


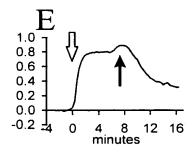
Fig 3

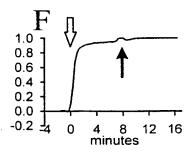


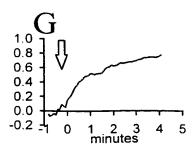












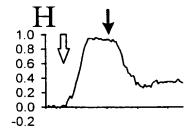


Fig 4

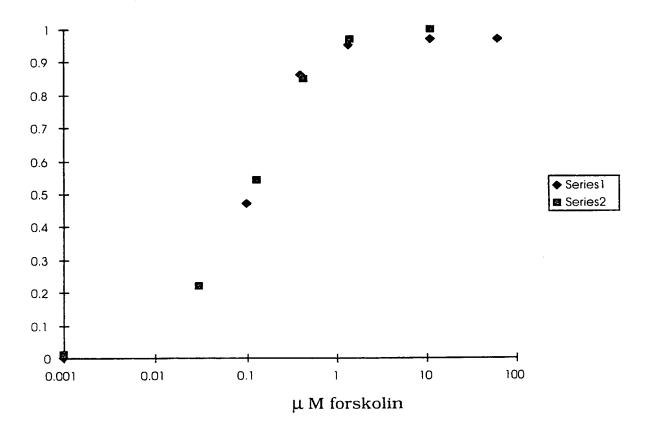


Fig 5

[forskolin]µM	$t_{1/2\text{max}}/s$	t _{max} / s
1	115±21	310±31
10	69±14	224±47
50	47±10	125±28

Fig 6

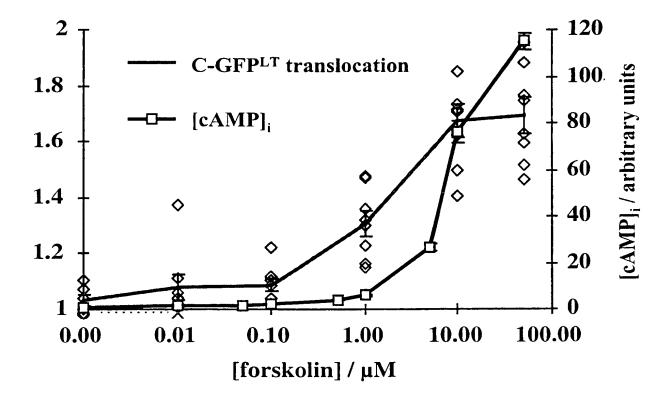
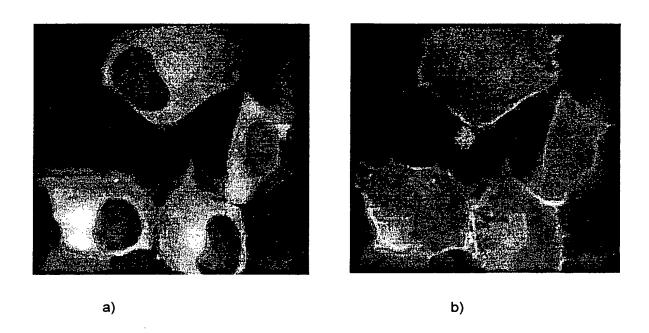


Fig 7



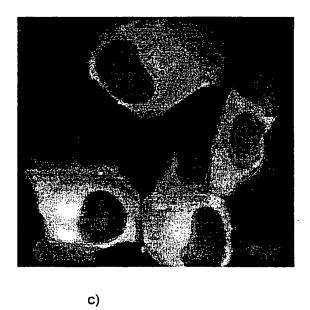
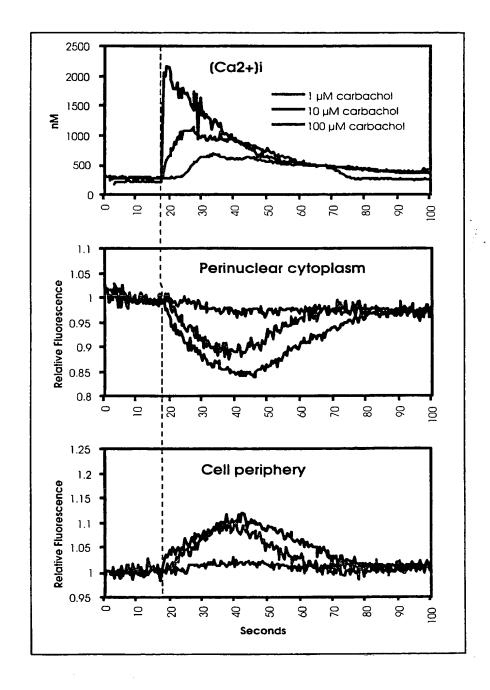
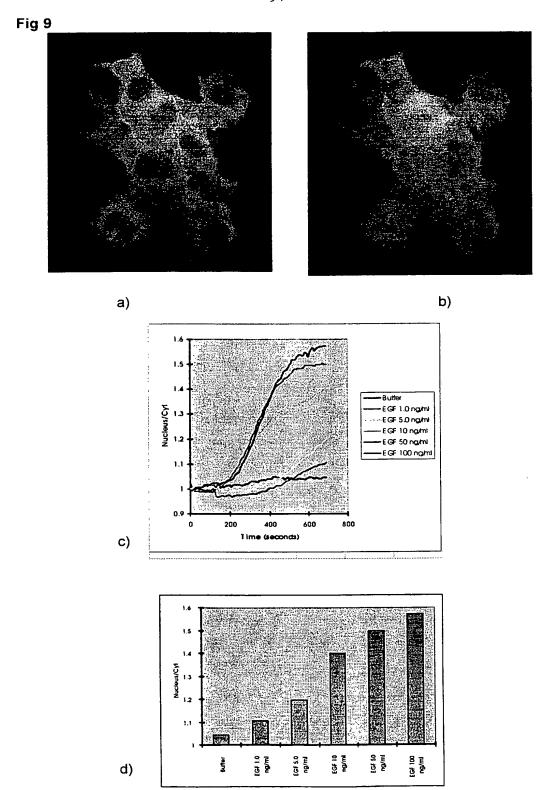


Fig 8

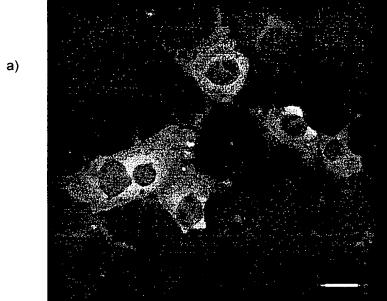


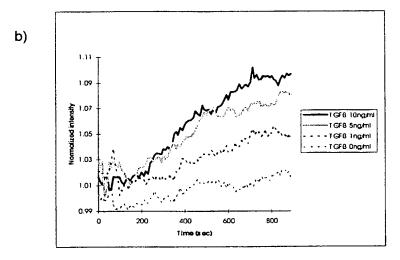


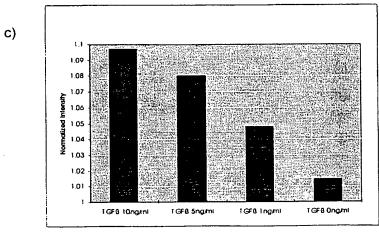
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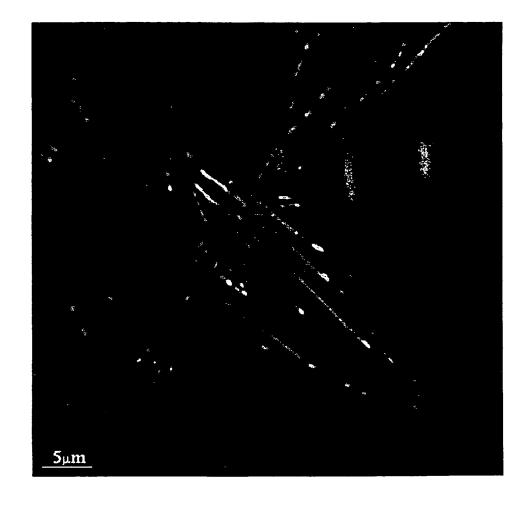




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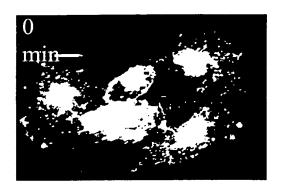
Fig 11



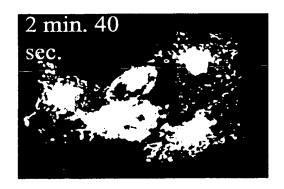
WO 98/45704 PCT/DK98/00145

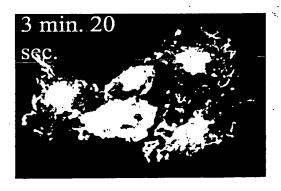
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Fig. 12













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#### (57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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CLASSIFICATION OF SUBJECT MATTER
C 6 G01N33/50 C120 IPC 6 C12Q1/48 C1201/25 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 6 GO1N C12Q C12N C07K Decumentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X WO 97 11094 A (NOVONORDISK AS ; THASTRUP 1-27 OLE (DK); TULLIN SOEREN (DK); POULSEN LAR) 30-40.44-60. 27 March 1997 64-82,88 see the whole document Υ see claims 28,29, 41,61-63 WO 91 01305 A (UNIV WALES MEDICINE) X 1-27. 7 February 1991 30-40.42-60, 64-84, 87,88 see page 4, line 15 - line 20 Υ see claims 28,29, 41,61-63 see examples 1-10 -/-χ Further documents are listed in the continuation of box C. Patent family members are listed in annex. ³ Special categories of cited documents : T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the lart which is not considered to be of particular relevance." invention "E" earlier document but published on or after the international X document of particular relevance; the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) elocument of particular relevance; the claimed invention cannot be considered to involve an inventive step when the "O" document referring to an oral disclosure, use, exhibition or focument is combined with one or more other, such documents, such combination being obvious to all person skilled n the artin document published prior to the international filing date but later than the priority date claimed : : ::ment member of the same patent family Date of the actual completion of the international search " at- 11 mailing of the international search report **75**, 02, 1999 19 January 1999 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL · 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Hoekstra, S Fax: (+31-70) 340-3016

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Y	WO 96 23898 A (NOVONORDISK AS ;THASTRUP OLE (DK); TULLIN SOEREN (DK); POULSEN LAR) 8 August 1996 see the whole document	28,29, 41,61-63
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C.(Continu	iation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	SCHMIDT. D.J. ET AL.: "Dynamic analysis of alpha-PKC-GFP chimera translocation events in smooth muscle with ultra-high speed 3D fluorescence microscopy" FASEB JOURNAL, vol. 11, no. 3, 28 February 1997, page A505 XP002077257 cited in the application see abstract	1-43,46, 47,49, 53-57, 59-82,88
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In. .ational Application No PCT/DK 98/00145

CAREY K L ET AL: "EVIDENCE USING A GREEN FLUORESCENT PROTEIN-GLUCOCORTICOID RECEPTOR CHIMERA THAT THE RAN/TC4 GTPASE MEDIATES AN ESSENTIAL FUNCTION INDEPENDENT OF NUCLEAR PROTEIN IMPORT"  THE JOURNAL OF CELL BIOLOGY, vol. 133, no. 5, June 1996, pages 985–996, XP000670316 cited in the application see the whole document  COGAWA H ET AL: "LOCALIZATION, TRAFFICKING, AND TEMPERATURE-DEPENDENCE OF THE ACOUNTER GREEN FLUORESCENT PROTEIN IN CULTURES VERTEBRATE CELLS"  PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 92, no. 25, 5 December 1995, pages 11899–11903, XP002029556 see the whole document  COMESTPHAL, MONIKA ET AL: "Microfilament dynamics during cell movement and chemotaxis monitored using a GFP – actin fusion protein"  CURR. BIOL. (1997), 7(3), 176–183 CODEN:  CUBLEZ:ISSN: 0960–9822, XP002090291 see page 181, left-hand column, line 1  CODA, TAKASHI ET AL: "The fission yeast st55+ gene is required for maintenance of growth polarity and functionally interacts with protein kinase C and an osmosensing MAP kinase pathway"  J. CELL SCI. (1996), 109(9), 2331–2342  CODEN: JNCSAI:ISSN: 0021–9533, XP002090292 see abstract  WEBB, CHRIS D. ET AL: "Use of green fluorescent protein for visualization of cell-specific gene expression and subcellular protein localization during sporulation in Bacillus subtilis"  J. BACTERIOL. (1995), 177(20), 5906–11  CODEN: JOBAAY;ISSN: 0021–9193, XP002089513 see the whole document	C (Continu	STION DOCUMENTS CONSIDERED TO BE RELEVANT	PC17DK 98700145
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sts5+ gene is required for maintenance of growth polarity and functionally interacts with protein kinase C and an osmosensing MAP kinase pathway"  J. CELL SCI. (1996), 109(9), 2331-2342 CODEN: JNCSAI:ISSN: 0021-9533, XP002090292 see abstract  WEBB, CHRIS D. ET AL: "Use of green fluorescent protein for visualization of cell-specific gene expression and subcellular protein localization during sporulation in Bacillus subtilis"  J. BACTERIOL. (1995), 177(20), 5906-11 CODEN: JOBAAY;ISSN: 0021-9193, XP002089513 see the whole document  WO 94 23039 A (CANCER RES INST ROYAL ;MARSHALL CHRISTOPHER JOHN (GB); ASHWORTH AL) 13 October 1994	X	dynamics during cell movement and chemotaxis monitored using a GFP - actin fusion protein" CURR. BIOL. (1997), 7(3), 176-183 CODEN: CUBLE2;ISSN: 0960-9822, XP002090291	
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ational application No. PCT/DK 98/00145

Box I Observations where certain claims wer found un earchabl (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 83-84 and claim 87 relate to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy).  2. X Claims Nos.: 85,86
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
1. X As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  X The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

# International Application No. PCT/DK 98/00145 FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210 Claims Nos.: 85,86 The subject-matter (compounds per se) is solely characterised in claims 85 and 86 by the result to be achieved, no support of a technical character is derivable from the description for the technical formulation of the subject of the search, accordingly no scope of a search could be defined and a meaningfull search is hence not possible.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 47, 49, 53-57

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being serine/threonine protein kinases

2. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 48

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to tyrosine kinases

3. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 50, 51

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to cAMP dependent protein kinases.

4. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 52

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active

# FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being cGMP dependent protein kinases

5. Claims: Partially: 1-43, 59-82 and 88; Entirely: 58

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being protein phosphatases

6. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 44

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to transcription factors

7. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 45

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to proteins associated with the cytoskeletal network

Information on patent family members

Iri. Jational Application No PCT/DK 98/00145

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Form PCT/ISA/210 (patent family annex) (July 1992)

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